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Pathological Fractures in Rare Bone Diseases: Clinical Cases

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Abstract. Rare bone diseases, though uncommon, present significant diagnostic and therapeutic challenges due to their clinical variability and overlapping symptoms with more prevalent conditions. This article describes a clinical case series of three patients with bone fragility fractures caused by rare bone diseases – primary hyperparathyroidism with brown tumor, Gorham-Stout disease, and alkaptonuria – treated at the Department of Orthopedic and Traumatology of Pisa University Hospital between 2018 and 2023. Each case highlights the diagnostic complexities, including inconclusive biopsies, nonspecific imaging findings, and the necessity of a multidisciplinary approach for accurate diagnosis and management. Advanced imaging techniques, such as MRI, CT, and PET, alongside genetic and biochemical analyses, were instrumental in guiding treatment. The cases underscore the importance of early differential diagnosis, which is critical for optimizing both surgical and non-surgical interventions, preventing long-term complications, and improving the patient outcomes. This study emphasizes the need for a collaborative, multidisciplinary approach to effectively diagnose and manage rare bone diseases, ensuring that patients receive timely and appropriate care.

Keywords: pathological bone fractures, Alkaptonuria, Gorham-Stout, primary hyperparathyroidism, rare bone diseases.

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Patologiniai lūžiai retų kaulų ligų atveju: klinikiniai atvejai

Santrauka. Retos kaulų ligos vis dėlto kelia didelių diagnostinių ir terapinių sunkumų dėl klinikinio įvairiapusiškumo ir simptomų, kurie sutampa su dažniau pasitaikančių ligų simptomais. Šiame straipsnyje aprašoma trijų pacientų, kuriems buvo diagnozuoti retų kaulų ligų – pirminio hipertiroidizmo su ruduoju naviku, Gorhamo-Stouto ligos ir alkaptonurijos – sukelti kaulų trapumo lūžiai, klinikinė atvejų serija. Kiekvieno atvejo diagnostika sudėtinga, įskaitant neaiškias biopsijas, nespecifinius vaizdo tyrimų rezultatus ir būtinybę taikyti daugiadisciplininį požiūrį tiksliai diagnozei ir gydymui. Pažangios vaizdo gavimo technologijos, tokios kaip MRT, KT ir PET, kartu su genetinėmis ir biocheminėmis analizėmis, buvo labai svarbios nustatant gydymo kryptį. Šie atvejai pabrėžia ankstyvos diferencinės diagnozės svarbą siekiant optimizuoti tiek chirurgines, tiek nechirurgines intervencijas, užkirsti kelią ilgalaikėms komplikacijoms ir pagerinti pacientų gydymo rezultatus. Šiame tyrime pabrėžiama bendradarbiavimo ir daugiadisciplinio požiūrio būtinybė siekiant veiksmingai diagnozuoti ir gydyti retas kaulų ligas, užtikrinti, kad pacientai laiku gautų tinkamą priežiūrą.

Raktažodžiai: patologiniai kaulų lūžiai, alkaptonurija, Gorhamo-Stouto sindromas, pirminis hipertiroidizmas, retos kaulų ligos.

Introduction

Bone is a mineralized connective tissue composed of two components: cellular (osteoblasts, osteocytes, and osteoclasts) and extracellular (organic bone and mineral matrix). The cellular component guarantees the correct process of bone turnover while the extracellular component is responsible for the mechanical function and storage of calcium and phosphate. Despite its inert appearance, bone is a highly active tissue, continuously subjected to remodeling, which leads to replacement of the old tissue with the new one, guaranteeing the skeleton the ability to adapt to mechanical use, correct the calcium and phosphate homeostasis, and healing fractures. Remodeling is necessary for skeletal health, and is finely regulated by processes in which numerous local and systemic factors participate (cytokines, hormones, intracellular signals, and biomechanical stimulation).[1,2] An imbalance between bone resorption and new bone formation determines bone fragility, a pathological condition in which the correct bone microarchitecture is altered, the resistance of the bone tissue is reduced, and the skeleton is subject to deformities and fractures, even in the presence of mild or no trauma.[3,4] While bone remodeling is a well-coordinated and vital process for bone health, any alteration can lead to bone impairment; this can contribute to a range of skeletal disorders, including rare diseases. A disease is defined as 'rare' when it has a prevalence of 7.5/100,000, or when it affects fewer than 5/10,000 individuals. More than 6000 rare diseases are described, and EURORDIS (Rare Diseases Europe) estimates that less than 80% of rare diseases have a genetic cause.[5] Rare diseases that affect the musculoskeletal system, although representing a small percentage compared to common bone pathologies, are characterized by heterogeneous clinical and radiological manifestations which are often chronic and disabling, resulting in a worsening of the patient's quality of life. Due to their rarity and the lack of specific therapies, these diseases require early diagnosis and often multidisciplinary management, even if, in most cases, there are no specific therapies; additionally, clinical symptoms, imaging and histological examination are often not specific and diagnostic – which makes it difficult to establish a correct diagnosis. Genetic diseases involving the skeletal system represent a considerable part of known rare diseases, and the IOF (International Osteoporosis Foundation) [6] has recently classified rare diseases into four main groups based on their primary pathogenic mechanism: alteration of cellular function (osteoblasts, osteoclasts, or osteocytes), alteration of the function of bone matrix proteins, and alteration of hormones that regulate calcium.

Alteration of cellular function

This first group includes diseases in which the primary problem is an alteration in the cellular function of the cells that build, remodel, or maintain bone: osteoblasts (which produce the bone matrix), osteoclasts (which resorb the bone matrix), and osteocytes (cells 'trapped' in the bone matrix, which perform regulatory functions). Within this category, there are subcategories that include: reduced bone resorption; increased bone resorption; high bone formation; and decreased bone formation.

Altered bone matrix proteins

In this group, the main problem concerns structural components of the bone matrix: proteins that are part of the bone's 'scaffolding', its mineralization, and the quality of collagen. Subcategories include disorders of collagen metabolism; defects in collagen proteins that compromise the mechanical strength of the bone; and disorders of the enzyme alkaline phosphatase.

Altered bone microenvironmental regulators

This third group includes diseases in which the defect lies not in the bone cell or matrix itself, but in the regulators that control bone cells and their microenvironment: cytokines, growth factors, and receptors. Subcategories include disorders of the RANK/RANKL/OPG system; disorders of the glycophosphatidylinositol biosynthesis pathway; disorders of the LRP5 receptor; and disorders of the bone morphogenetic factor receptor.

Deranged calciotropic hormonal activity

The fourth group includes diseases in which the central problem is an alteration in the hormonal or metabolic regulation of calcium, phosphate, or vitamin D, which, in turn, impacts bone metabolism. Subcategories include excess or deficiency of parathyroid hormone or altered PTH receptor signaling; disorders of vitamin D metabolism and action; and disorders of phosphate homeostasis that affect bone mineralization.

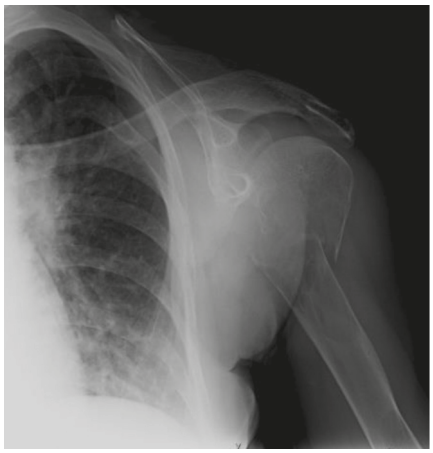
Pathological fractures are mostly tumor related; nevertheless, orthopedic surgeons must consider other potential causes in order to reach a correct diagnosis. In this article, the authors describe a clinical case series of three patients affected by bone fragility fractures due to rare bone diseases, conducted at the Department of Orthopedic and Traumatology of Pisa University Hospital between 2018 and 2023; the aim of this study is to analyze the clinical, diagnostic and therapeutic characteristics and hitches of each case to highlight the importance of an early differential diagnosis with the objective to optimize both surgical and non-surgical treatment.

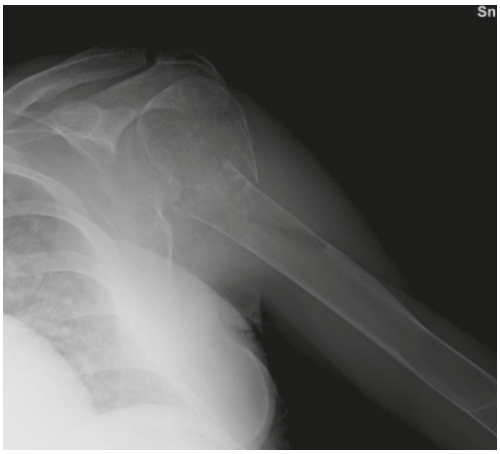
Clinical Cases

Case 1

A 23-year-old female patient was admitted to our Hospital in October 2018 for spontaneous fracture of the left proximal humerus during delivery, which occurred a few days previously.

The patient was completely asymptomatic before the labor. Plain X-ray (Fig. 1 and 2) showed a pathological fracture at the proximal humeral metaphysis with the surrounding osteolytic area. The total body TC (Fig. 3) scan confirmed these findings, revealing other similar lesions at distal humerus, ribs, scapula and left iliac crest. RM study (Fig.4) of the left arm showed a multi-lobulated, fluid filled, lytic lesion in the site of fracture. Bone scintigraphy (Fig. 5) showed multiple similar areas of accumulation of radionuclides in the same site found with a TC scan.





Figures 1 and 2. X-ray with a pathological fracture at the proximal humeral metaphysis with the surrounding osteolytic area

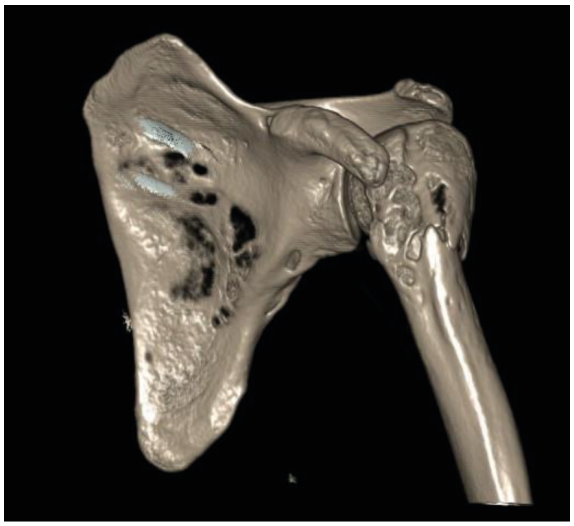


Fig. 3. TC 3D of proximal humeral fracture

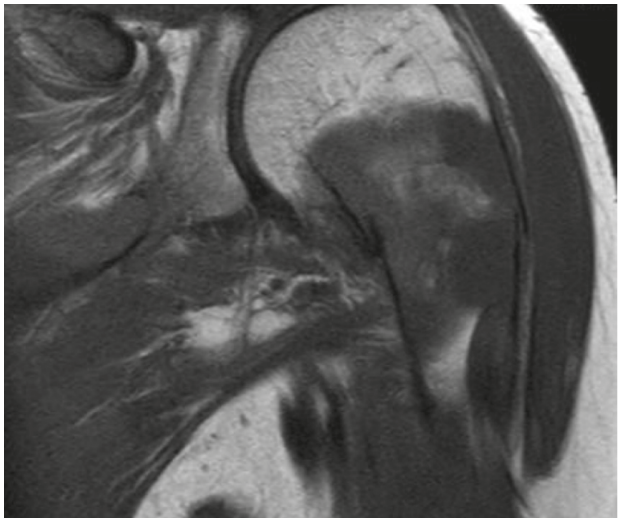


Fig. 4. RM study of the left arm showed a multi-lobulated, fluid filled, lytic lesion in the site of fracture

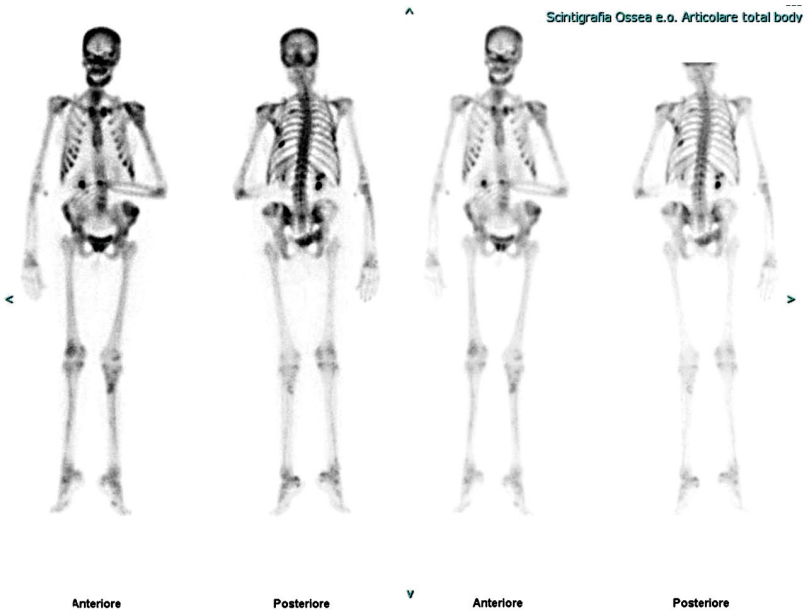


Fig. 5. Bone scintigraphy showed multiple similar areas of accumulation of radionuclides in the same site found with TC scan

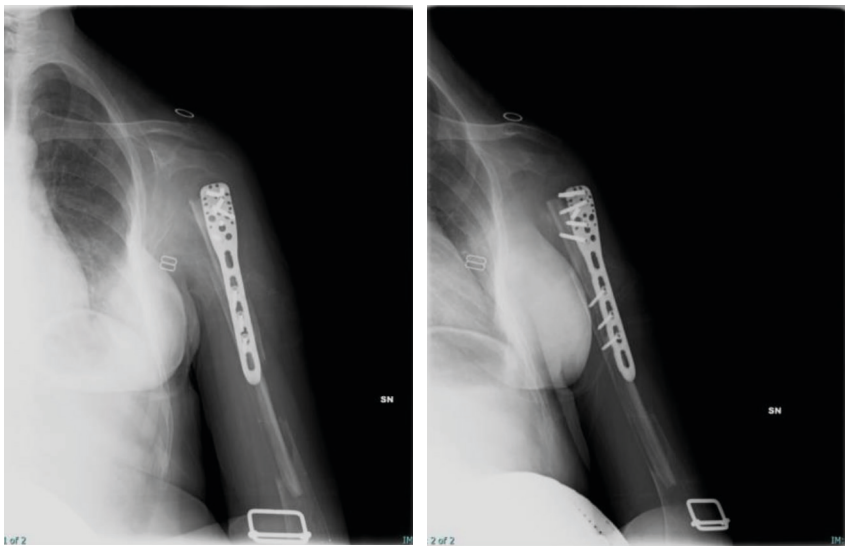


Fig. 6. Routine X-rays at 30 days from surgery showed near complete resorption of the left humeral head, without implant mobilizations signs or pain

The biggest lesion, at the left iliac crest, was biopsied, taking tissue samples from the wall of the cyst. The extemporaneous histological examination result was compatible with an aneurysmal bone cyst. Routine pre-operative laboratory analyses demonstrate hypercalcemia: the total serum Calcium was 11.2 mg/dL (range 8.6–10.2).

This finding was initially erroneously interpreted as a consequence of the multiple osteolytic lesions and the pathological fracture itself. Serum creatinine was 0.30 mg/dL, whereas serum Mg, P, PTH were not included in the routine analyses.

The fracture needed a rapid reduction and fixation; consequently, the patient underwent an urgent surgical procedure consisting in curettage of the proximal humerus and the subsequent fracture fixation using fibular allografts, a plate, and screws. Final histological results on the surgical material confirmed the diagnosis of multifocal solid aneurysmal bone cysts. After the procedure, the shoulder was immobilized for 30 days in a brace. The patient was discharged in a few days in good condition. We observed a normalization of routine laboratory analyses, especially the serum calcium level (value at discharge: 9.6 mg/dL), even if was not corrected for the serum albumin values.

Routine X-ray at 30 days from the surgery showed near complete resorption of the left humeral head, without implants mobilizations signs; pain was not experienced by the patient (Fig. 6).

New blood exams were prescribed: hypercalcemia (11.6 mg/dL, range 8.6–10.2); hypophosphatemia (2.0 mg/dL, range 2.5–4.5), very high levels of PTH (610 ng/L, range 8–40); low serum 25-OH vitamin D3 (<4mcg/L, normal if >30), normal magnesemia (2.1 mg/dL, range 1.7–2.5); low-normal serum creatinine 0.43 mg/dL (range 0.5–0.9); normal total serum proteins (7.5 g7dL) and albumin (4.5 g/dL, range 4.5–5); low-normal serum calcitonin (<2 ng/L, normal if <11.5). Mineralometry (DEXA) was performed, demonstrating diffuse reduction of the bone mineral density. Considering the evident altered blood calcium phosphorus ratio, the pathologist re-examined the histological samples and, underlining the challenging differential diagnosis, did not exclude a brown tumor lesion. A primary hyperparathyroidism was strongly suspected; hence, parathyroid ultrasonography and endocrinologic evaluation were performed, which highlighted a hyperplastic left-inferior parathyroid with high vascularization.

Intense hydration was instituted to control hypercalcemia (no symptoms were ever recorded). In December 2018, about two months after the surgery, the patient underwent selective parathyroidectomy with rapid normalization of the electrolyte and hormones serum levels. Histological examination confirmed the diagnosis of adenoma of the parathyroid gland.

The patient's shoulder was immobilized in a brace for another month, and then, at 90 days, a rehabilitation programme was prescribed. Shoulder X-rays were performed every 30 days for the first 6 months, demonstrating a low but progressive re-calcification of bone, and no mobilization signs of the implants. No other complications were reported. At 6 months after the surgery, a total body TC scan showed no new bone lesions as well as partial reduction of the pre-existing ones.

The symptoms completely resolved, and left shoulder articularity reached about 140° of anterior elevation and 130° of abduction, with intra and extra rotations only slightly restricted. At 10 months after the surgery, the patient did not have any limitation in daily activities, and thus she could take care of her baby completely. She has been periodically evaluated by the endocrinologists as a normal follow-up procedure.

Case 2

A 42-year-old man, with no history of oncological diseases, reported blunt trauma to his left shoulder in December 2020 resulting in pain and limitation of shoulder mobility. After a clinical and radiological evaluation, he was admitted to the orthopedics department for further investigations. The instrumental tests performed (Fig. 7), including a CT scan (Fig. 8) of the upper limb, revealed a pathological fracture. MRI examination of the shoulder showed an expansive lesion of the proximal humerus, with infiltration of the adjacent soft tissues, including the triceps and deltoid (Fig. 9). Initial

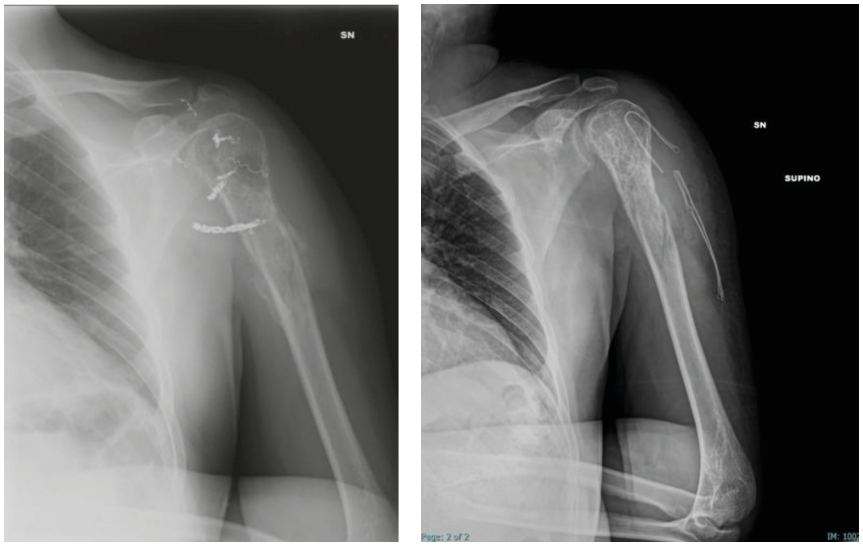


Fig. 7. X-rays with a pathological fracture at the proximal humeral

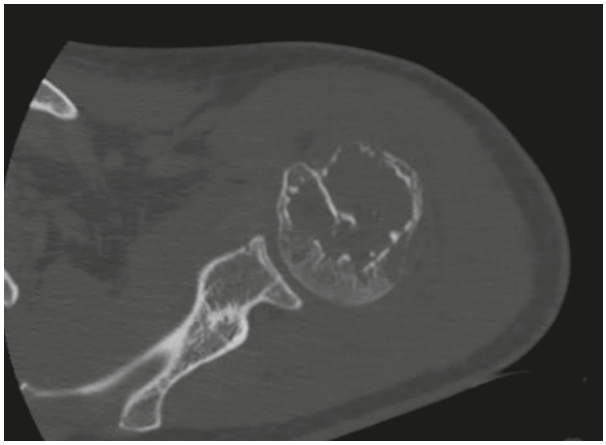


Fig. 8. TC scan of proximal humeral with pathological fracture

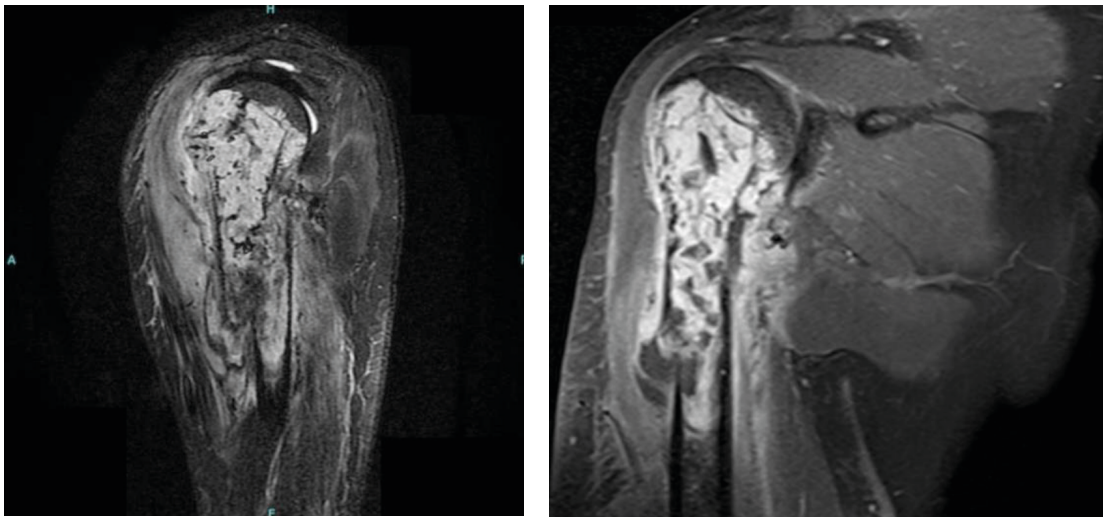


Fig. 9. MRI examination of the shoulder showed an expansive lesion of the proximal humeral, with infiltration of the adjacent soft tissues, including the triceps and deltoid

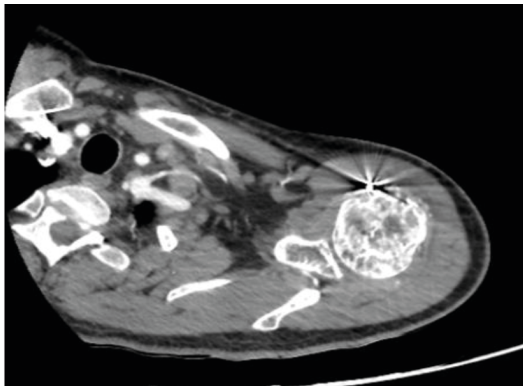


Fig. 10. TC scan of subsequent biopsy of proximal humeral

imaging was consistent with a diagnosis of osteosarcoma. Furthermore, a PET examination showed significant hyperuptake at the left proximal humerus (SUV max 5.01), retropectoral lymph node (SUV max 5.72) and axillary lymph node (SUV max 3.70), suggesting a possible regional dissemination. In January 2021, the patient was centralized and admitted to our hospital; he underwent an incisional biopsy of the lesion, which, however was non-diagnostic because of copious local bleeding from the lesion. During the hospital stay, a thoraco-abdominal CT scan for staging was performed, which showed no evidence of metastatic lesions in the areas examined. Subsequently, local imaging tests (MRI and CT) were performed, which confirmed the presence of a proximal meta-diaphysis osteolytic lesion of the left humerus, with partial sparing of the epiphysis. The lesion, approximately 13 cm in size, showed signs of hypervascularization and small islands of adipose tissue. The bony cortex appeared worm-eaten with large interruptions and invasion into the adjacent soft tissues, but without obvious signs of metastatic spread. A serum protein electrophoresis performed later was normal, ruling out pathologies such as multiple myeloma or other hematologic malignancies. The patient then underwent embolization of the blood vessels feeding the lesion to reduce vascularity and facilitate a subsequent biopsy (Fig. 10). Despite this, the subsequent biopsy did not provide a definitive diagnostic answer. Two months later, the patient was readmitted to our hospital for further clinical-radiographic evaluation, which confirmed the persistence of the osteolytic lesion. He then underwent a new embolization, and, subsequently, surgical curettage. The material obtained was subjected to histological examination, which reported "abundant blood material, flaps of granula-

tion tissue and areas of fracture callus". Given the overall findings, progressive osteolysis, a hypervascularized lesion, absence of malignancy, and exclusion of other causes (neoplastic, inflammatory, or metabolic), a diagnosis of Gorham-Stout disease was made. The patient subsequently underwent additional therapeutic embolizations, with progressive improvement in mobility and stabilization of the radiological findings. At follow-up, no significant progression or appearance of secondary neoplastic lesions was observed.

Case 3

A 63-year-old socially active woman employed in a corporate setting presented to our hospital in January 2021 for an episode of right knee pain (predominantly under load) associated with marked weakness. She reported that the pain had developed suddenly, without any history of direct trauma or fever. The patient had previous surgical interventions of cholecystectomy and bladder stones that occurred 25 and 15 years ago, respectively, as well as being affected by osteoporosis and rheumatoid arthritis undergoing pharmacological treatment. Therefore, radiographic examinations were performed, in which, multiple and bilateral lytic aerators were found, mainly represented in the diaphysis region of the femur, tibia and fibula associated with marked arthritic narrowing. In the suspicion of multiple myeloma, blood tests were also performed, which were found to be normal, and further instrumental investigations were implemented. MRI of the lumbosacral spine and legs bilaterally revealed a lesion at the level of the tibia and fibula bilaterally with multiple hypointense signal alterations of a lytic nature of suspected pathological nature; with posterior disc bulging in the L3-S1 tract in the absence of vertebral collapse. In addition, a PET examination (Fig. 11) showed a mild hyperuptake (SUV max 3) at the level of the middle third of the diaphysis of both femurs and a marked increase in metabolic activity affecting the articular cartilages of both knees; although it was suspected of being of inflammatory nature. Considering the clinical-instrumental picture, in February 2021, the patient underwent CT-guided tibial needle biopsy (Fig. 12 and 13), which was negative for neoplastic pathologies. In February 2022, however, the patient visited our Emergency Department for an acute onset of pain in the left hip with inability to bear weight. After a complete clinical and radiological evaluation, she was admitted to the orthopedic department for further investigation. Imaging studies revealed a left femoral trochanteric fracture, associated with the presence of osteolytic areas, suggesting an underlying pathological process. The fracture was stabilized and re-

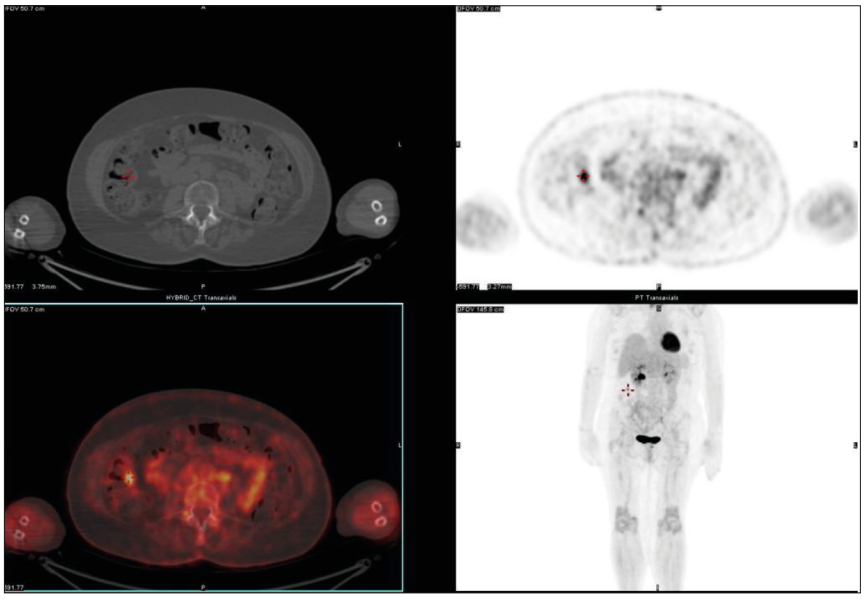
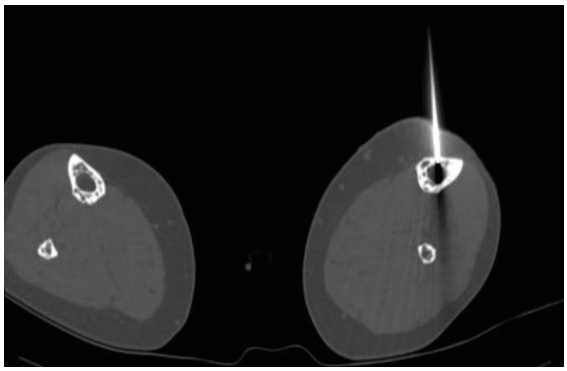
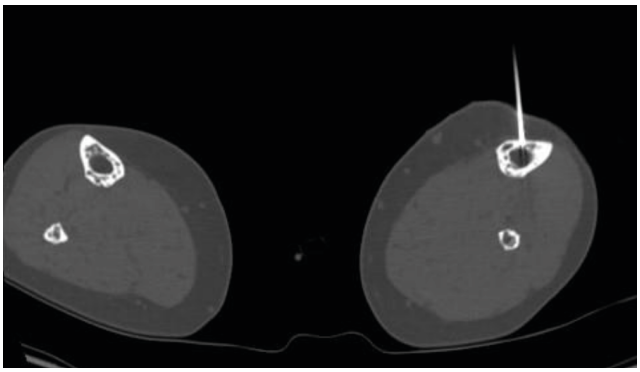
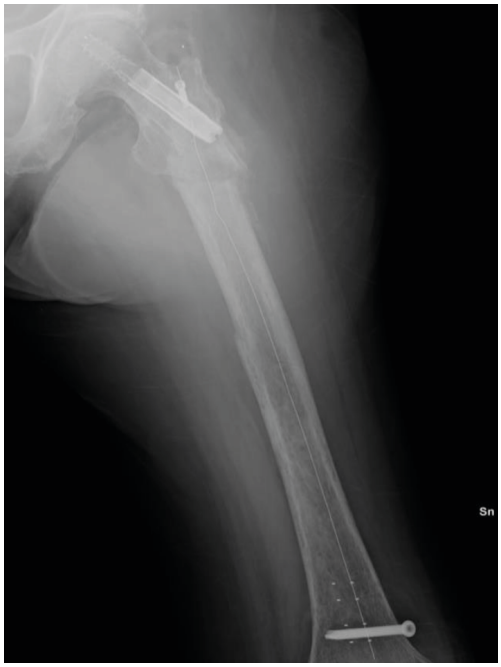


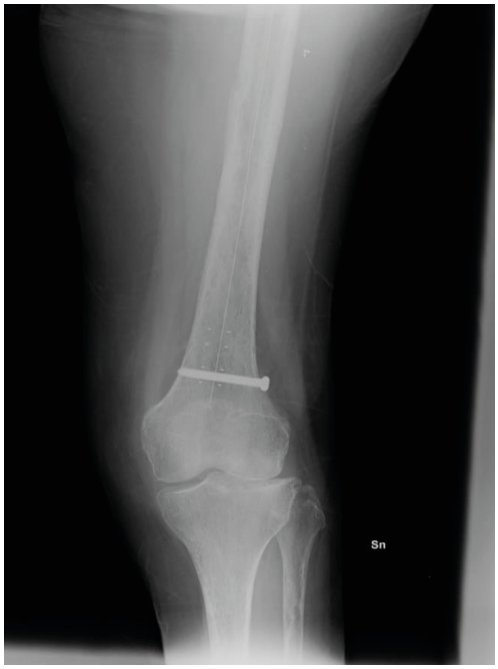
Fig. 11. PET examination showed a mild hyperuptake (SUV max 3) at the level of the middle third of the diaphysis of both femurs and a marked increase in metabolic activity affecting the articular cartilages of both knees

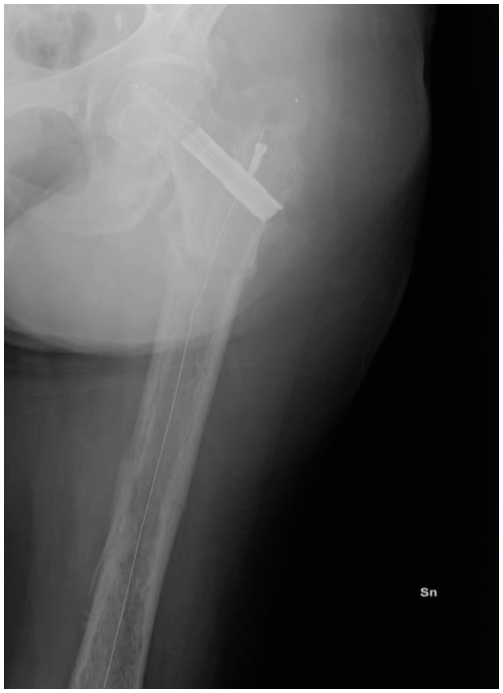




Figures 12 and 13. CT-guided tibial needle biopsy







Figures 14, 15 and 16. A left femoral trochanteric fracture stabilized and reduced with a carbon intramedullary nail

duced with a carbon intramedullary nail in the following days (Fig. 14, 15 and 16). During her hospital stay, no postoperative complications or alterations in blood tests and instrumental tests were observed. Postoperative follow-up evaluations revealed nonunion of the knees and hip, as well as multiple new-onset atraumatic vertebral fractures. The patient also reported previously undescribed characteristic clinical findings, such as darkening of the urine upon exposure to air, increased scleral pigmentation, and a bluish-gray coloration of the auricles that had been present since adolescence but had never been investigated. These findings prompted a multidisciplinary discussion, which led to further clinical, instrumental, and genetic testing. The diagnosis was finally confirmed by the detection of elevated levels of homogentisic acid (HGA) in the patient's urine, which was consistent with alkaptonuria. The patient's postoperative recovery was uneventful, and, at her last follow-up visit, several months after the surgery, she was able to stand without support, remaining independent in her daily activities and personal hygiene.

Discussion

Rare bone diseases, despite representing a relatively small percentage of overall skeletal pathologies, constitute a fascinating diagnostic and therapeutic challenge due to the difficult diagnosis determined by clinical variability and the overlapping of signs and symptoms with other more frequent pathologies. The diagnostic process in these diseases is often complicated by the fact that biopsy and histological results may be negative, or may not immediately correspond to the suspected condition. The three clinical cases of patients affected by rare conditions including primary hyperparathyroidism with brown tumor (BT), Gorham-Stout disease, and alkaptonuria, highlight how often, due to the overlap with more common pathologies of signs and symptoms such as bone fractures, joint pain and joint deformities accompanied with the scarcity of specific markers, the diagnosis can be extremely difficult and require, in addition to an in-depth clinical and instrumental evaluation, a diagnosis of exclusion. BT represents an extremely rare manifestation of late and uncontrolled HPT, resulting from rapid osteoclastic turnover of bone caused by abnormally increased PTH.[7] BT formation is associated with hemosiderin deposition in bone tissues, which can cause multiple lytic lesions and a radiological appearance similar to bone metastases.[8,9] Although, in most cases, the tumors are solitary, some cases of lesions at multiple sites have been reported. In patients presenting with multiple lytic lesions of the bone, the presence of BT should be considered as a differential diagnosis of malignant parathyroid metastasis. BT and bone metastases are seen in the skull, pelvis, ribs, and femur. Further common factors are haematochemical and instrumental tests such as high levels of Ca and PTH in serum, urolithiasis and increased foci of radiotracer absorption on skeletal scintigraphy, which can be found both in BT and in metastases. Although biopsy is considered the diagnostic gold standard, in many cases, it can prove to be inconclusive; therefore, the differential diagnosis between BT and malignant metastases is extremely challenging. The main causes of PHPT are parathyroid adenoma, which accounts for 85%, parathyroid hyperplasia, which accounts for 10–15%, and cancer, which accounts for 1–5%. Patients with PHPT often present with symptoms of hypercalcemia, such as bone pain, bone fractures, nephrolithiasis, abdominal groaning, psychic groaning, and even extreme complications, including cardiac arrhythmia or coma.[10-12] In our case, the diagnostic difficulty was fueled by the picture of pathological fracture of the humerus associated with multiple multidestructive bone lesions, first incorrectly confused with metastatic lesions and subsequently diagnosed as aneurysmal bone cyst due to histological results. Blood chemistry tests for bone metabolism highlighted a picture of primary HyperPTH in the patient, whereas parathyroid ultrasonography showed parathyroid hyperuptake. The patient's clinical improvement following the parathyroidectomy surgery associated with the normalization of calcium and PTH levels

confirmed the diagnosis of PHPT with BT, highlighting the importance of an accurate differential diagnosis between BT and metastasis.

It is also useful to underline that hypercalcemia is a very effective marker in the diagnosis of exclusion between BT and aneurysmal cysts. Both pathologies can present as bone lesions with similar radiological characteristics that can be confused. Among the distinguishing factors, we have radiographic aspects, with brown tumors that appear as large-area osteolytic lesions, sometimes multiple, with blurred borders localized in areas of high osteoclastic activity, such as the distal part of long bones. Aneurysmal cysts are characterized by presenting a multilocular or multicystic lesion with a 'cluster' or 'honey' appearance. X-ray and CT show areas of cavitation or intralesional fluids, and are often limited to a single site. MRI is crucial to correctly diagnose them, as it shows a multilocular appearance, with fluid components and varying degrees of signal intensity that reflect the hemorrhagic and fluid content of the cyst. Another important distinguishing factor is given by laboratory markers. Hypercalcemia is a hallmark of brown tumors, associated with increased parathyroid hormone (PTH), which reflects primary hyperparathyroidism. In aneurysmal bone cysts (ABC), calcium and PTH levels are usually normal unless there are associated comorbidities. Definitive diagnosis requires an integrated approach that includes radiological, laboratory and histological tests, combined with clinical evaluation and the patient's history.

Our case of Gorham-Stout (GSD), 'Phantom bone disease', deals with an extremely rare, non-hereditary condition characterized by progressive, generally lytic osteolysis which can affect the ribs, skull, clavicle, upper limbs, with lymphatic and vascular proliferation with stimulation of osteoclasts and inhibition of osteoblasts.[13,14] Although GSD can be suspected in patients with osteolysis and non-neoplastic bone lesions, the diagnosis is extremely complex and requires exclusion of all possible causes of osteolysis such as inflammation and pathologies such as multiple myeloma, lymphangiomatosis, lytic metastases of unknown primary tumors, Paget's disease, etc. Blood tests are generally negative, and there are no specific markers with the exception of alkaline phosphatase which may be elevated. [15,16] The biopsy examination, following the criteria of Heffez et al. [17] allows for an accurate diagnosis to be made, even if sometimes the histological examination may fail to highlight neoplastic lesions but exhibit exclusively highly vascularized tissue instead. The extensive osteolysis and soft tissue involvement observed on imaging, along with inconclusive biopsy results, and aggressive behavior of the lesion led to the use of embolization. It was considered a supportive treatment option by reducing the lesion supply, which results in a reduction in progression, preventing further bone destruction, and allowing for better surgical planning, if necessary. The diagnosis remains a diagnosis of exclusion, [18] and the treatment involves the management of pain associated with maintenance of the joint function associated with immunosuppressive medical therapy, [19] pharmacological support with antiresorptive agents [20] and possible radiotherapy (in refractory or aggressive forms). [21] The main surgical indications are in cases of displaced fractures, impending fractures or significant functional limitations associated with pain.

Alkaptonuria is a rare metabolic disorder caused by a defect in the enzyme homogenized dehydrogenase, which leads to the accumulation of homogentisic acid (HGA) in the urine and various body tissues. Diagnosis is often delayed because its signs and symptoms are progressive and easily confused with other more common diseases, such as osteoarthritis. [22] The presence of dark urine and scleral pigmentation are strong indicators of alkaptonuria and should be considered in the differential diagnosis when a patient presents with unexplained joint pain, osteoarthritis, and fractures. These early signs may direct further testing for homogentisic acid in the urine.

Recently, it has also been described that osteoporosis and fragility fractures, as in our case, are common in cases of alkaptonuria; in their survey, Ranganath and Cox [23] described osteopenia in 46.7%, and fractures in 53.3% of patients. Bone fragility in alkaptonuria can be both focal and gen-

eralized, due to different mechanisms of action. Focal bone fragility is probably caused by the stress shielding phenomenon due to the presence of ochronotic rigid cartilage. Generalized spontaneous osetoclastogenesis has also been described and could explain spine and femoral low bone mineral density in many ochronotic patients. Rare bone diseases are, therefore, frequently misdiagnosed as more common conditions, leading to inadequate treatments. The importance of collecting a complete clinical history, together with a careful evaluation of biochemical markers and radiological characteristics, is fundamental to correctly direct the course of treatment. The use of advanced imaging techniques is crucial for the diagnosis of rare bone diseases. MRI, CT and PET are complementary tools that allow to obtain a more detailed view of bone lesions and to better understand their nature. The diagnosis and management of rare bone diseases require a multidisciplinary approach involving various specialists. Collaboration between orthopedic surgeons, endocrinologists and geneticists is essential for correct evaluation and management. A multidisciplinary approach allows to integrate specific skills and to personalize treatment, thereby improving the therapeutic efficacy and the patient's quality of life. In these cases, a network between different specialists is essential to reach the correct diagnosis, and, consequently, a correct treatment. The crucial role of II° and III° level imaging techniques, such as MRI and PET, supported by biopsy, offers a complete diagnostic picture that can effectively guide the patient's treatment. An integrated and collaborative approach is essential for optimal management of rare bone conditions and to avoid misdiagnoses that could compromise the patient's quality of life. Our small-sized sample did not allow us to design a reliable diagnostic algorithm; however, our findings can suggest that a combination of blood tests not suggesting osteometabolic disease and histological absence of malignancies should orient to rare forms of bone non-oncological diseases.

Conclusion

Rare musculoskeletal diseases, such as alkaptonuria, Gorham-Stout disease and primary hyperparathyroidism, represent a major challenge not only for their rarity but also for the resulting diagnostic complexity. The article highlights how the diagnostic approach to these pathologies can be hindered by negative biopsy tests or those that suggest alternative diagnoses, thereby complicating the diagnosis. Our case series highlights how fundamental is the importance of an integrated multidisciplinary approach to clinical evaluation; the use of advanced diagnostic techniques and genetic analysis must also be highlighted. Despite the diagnostic complexity, an early diagnosis is fundamental in patient management, allowing the adoption of the best treatment, preventing long-term complications and guaranteeing an excellent quality of life.

Author contributions

Va. B.: conceptualization, methodology, formal analysis, investigation, visualization.
F. D. S.: conceptualization, methodology, formal analysis, investigation, writing – original draft preparation, writing – review and editing, visualization.
M. C.: conceptualization, methodology, writing – original draft preparation, writing – review and editing, visualization.
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L. O.: conceptualization, investigation, writing – original draft preparation, writing – review and editing, visualization.
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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript. All authors approved the submitted version and agree to be accountable for all aspects of the work.

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