EJCRIM
European Journal
of Case Reports
in Internal Medicine

PRIMARY LYMPHOMA ARISING IN PAGET'S DISEASE IN A PATIENT WITH PRIMARY HYPERPARATHYROIDISM

Mercedes De La Fuente[1], Marina Arroyo[2], Ana S. Collado[3], Elena C. Gallardo[2], Santiago Montes[3,5], José M. Olmos[1,4,5]

[1] Division of Internal Medicine, Hospital Universitario Marqués de Valdecilla, Santander, Spain
[2] Division of Radiology, Hospital Universitario Marqués de Valdecilla, Santander, Spain
[3] Division of Pathology, Hospital Universitario Marqués de Valdecilla, Santander, Spain
[4] Departament of Medicine and Psychiatry, University of Cantabria, Santander, Spain
[5] Valdecilla Research Institute (IDIVAL), Santander, Spain

Corresponding author's e-mail: mercedesdelafuentev@gmail.com

Received: 11/12/2024
Accepted: 16/12/2024
Published: 22/01/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Consent has been obtained from the patient for the publication of this case report and any accompanying images.

How to cite this article: De La Fuente M, Arroyo M, Collado AS, Gallardo EC, Montes S, Olmos JM. Primary lymphoma arising in Paget's disease in a patient with primary hyperparathyroidism. *EJCRIM* 2025;**12**:doi:10.12890/2025_004778

ABSTRACT

Background: Paget's disease of bone (PDB) is characterized by a disturbance of the balance between bone formation and bone resorption at one or more bone sites. Its neoplastic transformation to osteosarcoma of the bone has been widely cited in the literature; however, association with non-Hodgkin's lymphoma (NHL) is very uncommon. In addition, whereas the pathophysiological relationship between PDB and secondary hyperparathyroidism is well established, there is much debate about the association between PDB and primary hyperparathyroidism (PHPT).

Case Report: We present a case of NHL arising in pagetoid bone in a 56-year-old man, who was subsequently diagnosed with primary hyperparathyroidism (PHPT).

Discussion: The malignant potential of pagetoid bone is well known, with sarcomatous degeneration being the most common neoplasm. Therefore, when pain recurred in our patient, 3 years after treatment of PDB, the presumptive diagnosis was a sarcomatous degeneration of the pagetoid bone. However, bone biopsy revealed a primary lymphoma, an extremely rare association that has been described only in a few cases. In addition, PHPT is rarely associated with PDB, although a link between PHPT and an increased risk of malignancy has been suggested.

Conclusion: To the best of our knowledge, this is the first case of these three different bone diseases in the same patient. Further studies are needed to understand the possible molecular basis of the association among these diseases.

KEYWORDS

Hyperparathyroidism, Paget's disease of bone, lymphoma

LEARNING POINTS

- Sarcomatous degeneration is the most common primary bone neoplasm associated with Paget's disease of bone (PDB). However, primary lymphoma in pagetoid bone is unusual.
- The association between PDB and primary hyperparathyroidism is very rare.
- The uniqueness of this case lies in coexistence of three bone diseases in the same patient.

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

INTRODUCTION

Paget's disease of bone (PDB) is the second most common disease of bone metabolism after osteoporosis. It is characterized by localized areas of accelerated, disorganized, and excessive bone production and turnover. Almost any bone can be affected, but there is a predilection for the pelvis, spine, femur, tibia, and skull[1]. Paget's disease is more common in males and in certain ethnic groups. Whites are the most commonly affected and it is estimated that the disease occurs in approximately 1% of people over 55 years of age in European countries.

Neoplastic transformation of the lesions is a rare complication of PDB, which affects about 0.3% of patients. The majority of these malignancies are sarcomas, with osteosarcoma by far the most common[2].

Documented cases of primary lymphoma of bone (PLB) associated with preexisting Paget's disease in that same bone, has been described on rare occasions[3]. Primary hyperparathyroidism (PHPT) is rarely found in patients with PDB, although it has been suggested that these patients may have an increased risk of secondary and tertiary hyperparathyroidism[4]. Additionally, coexistence of PHPT and non-Hodgkin lymphoma (NHL) has also been described, although whether is incidental or related has not been elucidated[5].

We present a case of MHL arising in pagetoid bone in a patient who was subsequently diagnosed with PHPT.

CASE DESCRIPTION

A 56-year-old white man who had experienced 3 months of progressive left pretibial pain following a blow to the left leg was referred to our clinic. He had a history of congenital ankylosis of the hands and bilateral deafness. The physical examination was remarkable only for a small painful lump in the left pretibial area. Neither lymphadenopathy nor hepatosplenomegaly was seen. Routine laboratory data were normal. Total skeleton bone scintigram, computed tomography (CT) scan, and magnetic resonance imaging (MRI) were subsequently obtained *(Fig. 1 and 2)*. These images revealed isolated skeletal abnormalities in the left leg. A CT-guided biopsy was performed, and histopathological findings were compatible with monostotic PDB *(Fig. 3)*. He was treated with zoledronate with remission of pain. Three years later, recurrent pain began in the same area. Follow-up plain radiographs, CT and MRI, showed that the lytic and soft tissue component had progressed *(Fig. 4)*, so a new CT-guided bone biopsy was performed, revealing a large cell lymphoma of bone with centroblastic morphology *(Fig. 5)*. He was treated with rituximab, cyclophosphamide, hydroxydaunomycin, oncovin, prednisone (R-CHOP) and a new dose of zoledronate, with a good response. Two years later, hypercalcemia (albumin-corrected calcium: 10.7 mg/dl, ionized calcium 1.48 mM), hypophosphatemia (1.9 mg/dl) and hypercalciuria (335.5 mg/24 hours) was detected. PTH levels were raised (246 pg/ml). Cancer antigens were

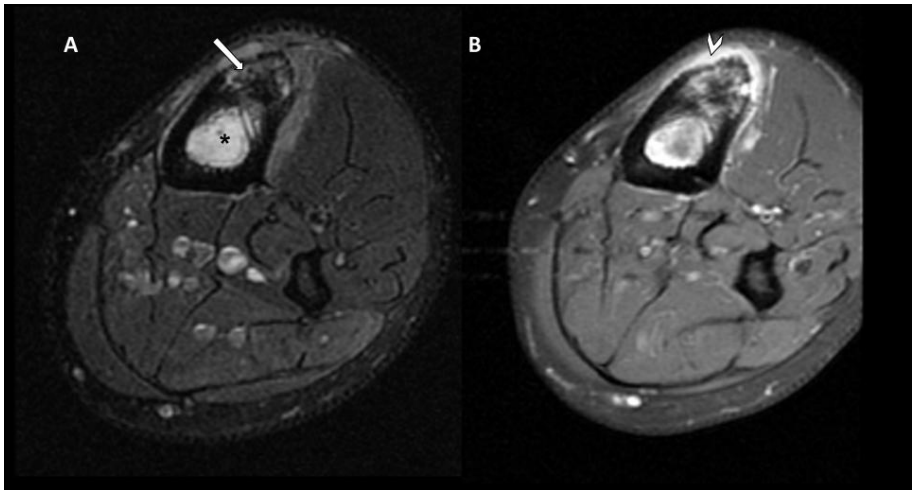

Figure 1. A) Axial proton density sequence magnetic resonance imaging and B) fat-saturated contrast-enhanced T1-weighted images. Bone marrow signal alteration (*), hyperintense in proton density sequences, thickening of the anterior cortex of the tibia with patchy areas of lower intracortical bone density (arrow) and soft tissue component enhancing after contrast administration (arrowhead).

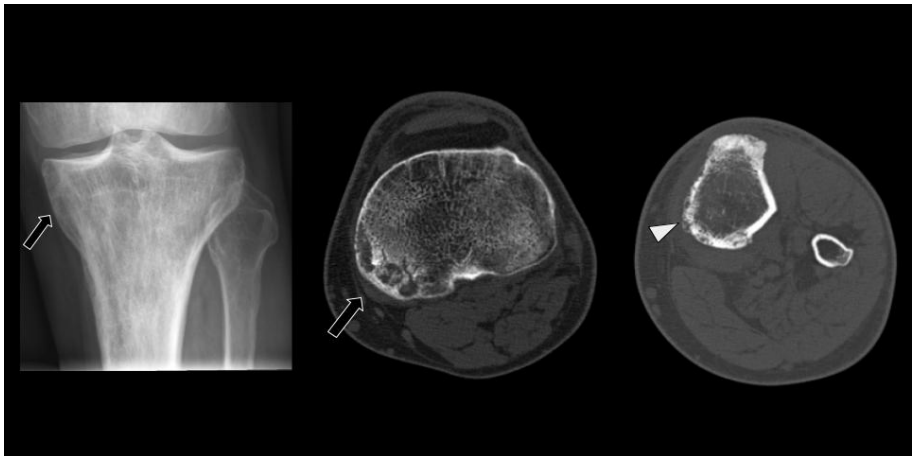

Figure 2. X-ray and computed tomography scan of the leg. Thickening of the anterior cortex of the tibia with patchy areas of reduced intracortical density (white arrows).

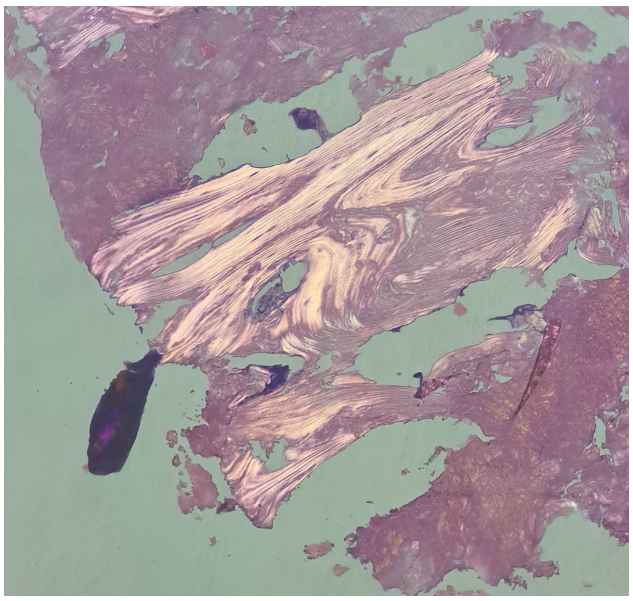

Figure 3. Bone biopsy (haematoxylin and eosin, H&E) showing a pattern of disorganised (mosaic) osteogenesis with polarised light characteristic of Paget's disease of bone.

negative, while other laboratory tests were normal. Further investigation with parathyroid scan was compatible with a right lower parathyroid adenoma. After surgical removal of the adenoma, biopsy confirmed the diagnosis. Presently, 1 year later, the patient remains relapse free, and he is asymptomatic.

DISCUSSION

The malignant potential of pagetoid bone is well known. Malignant neoplasms associated with PDB are most often metastases, and, rarely, primary malignant transformations. Sarcomatous degeneration is the most common of these, although it is actually a rare complication of PDB which affects about 0.3% of patients[1]. Primary lymphoma of the bone arises from the medullary cavity and presents as a focal, solitary lesion, which is extremely rare and only represents around 3% of primary bone malignancies and 1% of lymphoma[6]. Therefore, it is not surprising that lymphomatous complication of PDB has been rarely observed. Although other cases of bone lymphoma associated with PDB have been described, they were diagnosed more than 40 years ago, so the classification of lymphoma would be difficult to establish with current diagnostic criteria[6]. Given the low frequency of this association, it is difficult to determine in this case whether there was actually lymphomatous transformation of PDB or fortuitous coexistence of these two diseases.

Overproduction of PTH is reported in 12-18% of PDB[4]. Whereas the pathophysiological relationship between PDB and secondary HPT is well established[7,8], the aetiology of the association of PDB and primary HPT is a matter of debate. In fact, adenoma or hyperplasia of the parathyroid glands is rarely found in patients with PBD. The estimated prevalence is 2.2-6% based on large PBD cohorts, with more women being affected than men, a prevalence similar to or slightly higher than that in the general population, between 1 and 3% in men and women over 60 years old, suggesting that there is no etiologic link between the two disorders. However, the fact that *SQSTM1* gene, which is involved in the pathogenesis of PBD, and multiple endocrine neoplasia type 1 (MEN 1), share the same signalling pathway through nuclear factor kappa beta (NF-kB), raises the possibility that there could be a connection between PBD and PHPT[7,8]. Besides, several studies have shown a link between hyperparathyroidism and an increased risk of malignancy, including lymphoma[5]. Whether the coexistence of PHPT associated with lymphoma is incidental or related has not been elucidated. Studies have shown that *CDKN1B* mutations, a gene that encodes P27 protein, a member of the CDK inhibitor (CDKI) family that regulates cell cycle progression, could play a role as susceptibility genes for sporadic PHPT lymphoma, and other tumours[9].

CONCLUSION

The association of NHL and PHPT with PDB are rare. Nevertheless, it is advisable to be vigilant, and to investigate bone metabolism parameters in patients with PDB, as a means of monitoring the activity of the disease, the response to treatment and identification of the other underlying bone pathologies. It is unknown if there is any mechanism that can link these three diseases.

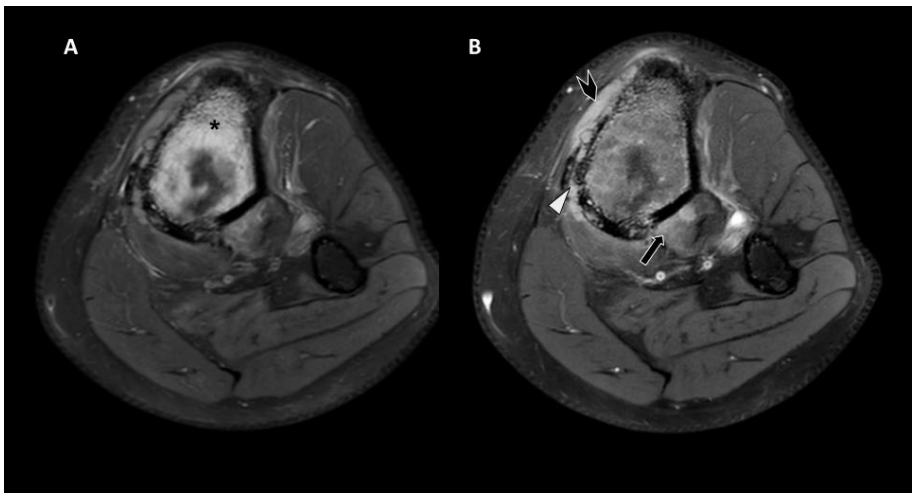

Figure 4. A) Axial proton density sequence magnetic resonance imaging and B) fat-saturated contrast-enhanced T1-weighted images. Extension of the eccentric lytic cortical lesion accompanied by permeation of the cortex not visible in previous studies (white triangle). Increase of the soft tissue component (black arrowhead). There is also enhancement of the adjacent musculature (black arrow). Bone marrow signal alteration persist (asterisk).

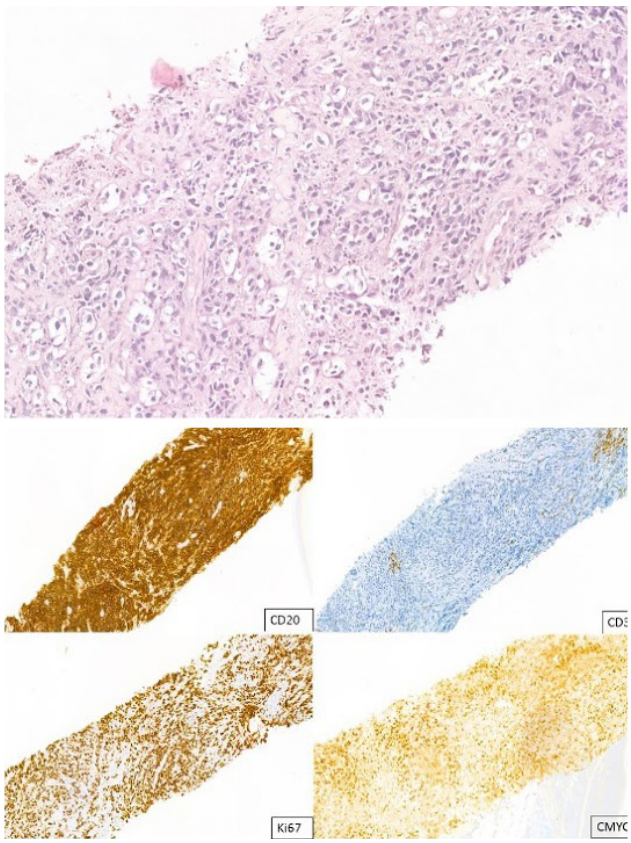

Figure 5. Computed tomography-guided bone biopsy. A) Soft tissue biopsy (H&E, ×20) with diffuse infiltration by intermediate and large lymphoid cells of centroblastic morphology. Sclerosis bands are observed around cells. B) Immunohistochemistry shows expression for b-lymphoid cells markers (CD20) and a residual T-cell component (CD3+). The proliferation index (Ki67) is > 80%, associated with overexpression of the C-MYC oncogene (> 40%).

REFERENCES

1. Ralston SH, Corral-Gudino L, Cooper C, Francis RM, Fraser WD, Gennari L, et al. Diagnosis and management of Paget's disease of bone in adults: A clinical guideline. *J Bone Miner Res* 2019;**34**:579-604.
2. Van Staa TP, Selby P, Leufkens HG, Lyles K, Sprafka JM, Cooper C. Incidence and natural history of Paget's disease of bone in England and Wales. *J Bone Miner Res* 2002;**17**:465-471.
3. Stephens GC, Lennington WJ, Schwartz HS. Primary lymphoma and Paget's disease of the femur. *Am J Clin Pathol* 1994;**101**:783-786.
4. Rendina D, De Filippo G, Merlotti D, Di Stefano M, Mingiano C, Giaquinto A, et al. Increased Prevalence of Nephrolithiasis and Hyperoxaluria in Paget Disease of Bone. *J Clin Endocrinol Metab* 2020;**105**:e4430-8.
5. Deng Y, Wang J, Liu H, Liu J, Xu J. Primary hyperparathyroidism associated with non-Hodgkin lymphoma: a case report and literature review. *Postgrad Med* 2020;**132**:398-401.
6. Wang WJ, Omo-Ogboi AC, Rivera X, Moosvi AM, Chen L. Bone primary, spindle cell variant of diffuse large B-cell lymphoma presenting in the femur from a Paget's disease patient. *Leuk Lymphoma* 2022;**63**:1765-1767.
7. Yu T, Squires F, Mammone J, Di Marcangelo M. Lymphoma arising in Paget's disease. *Skeletal Radiol* 1997;**26**:729-731.
8. Stathopoulos IP, Trovas G, Lampropoulou-Adamidou K, Benetos IS, Vamvakidis K, Vlachodimitropoulos D, et al. Coexistence of Paget disease of bone and primary hyperparathyroidism; a diagnostic challenge. *J Musculoskelet Neuronal Interact* 2013;**13**:255-258.
9. Alrezk R, Hannah-Shmouni F, Stratakis CA. MEN4 and CDKN1B mutations: the latest of the MEN syndromes. *Endocr Relat Cancer* 2017;**24**:195–208.