CLINICAL ONCOLOGY JOURNAL

Clinical Oncology Journal

ISSN: 2766-9882

Primary Hyperparathyroidism Associated with Osteosarcoma: A Case Report

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Article Type: Case Report

Compiled date: December 09, 2022

Volume: 3

Issue: 2

Journal Name: Clinical Oncology Journal

Publisher: Infact Publications LLC

Journal Short Name: Clin Oncol J

Article ID: INF1000237

Keywords: Hyperparathyroidism; Osteosarcoma; Parathormone; Hypercalcemia

Cite this article: Sawsen N, Taieb A, Asma BA, Ghada S, Ahlem B, Molka C, et al. Primary hyperparathyroidism associated with osteosarcoma: a case report. Clin Oncol J. 2022;3(2):1–4.

Abstract

Primary Hyperparathyroidism is a common endocrine disorder, often discovered fortuitously in the presence of hypercalcemia. Its association with Primary Osteosarcoma (PO) in some cases of the literature raises the hypothesis of a link between the two pathologies. We herein report a rare case of an ectopic parathyroid adenoma concomitant with the diagnosis of osteosarcoma.

A 40-year-old woman with a one-year history of low back pain and recent pain in her upper thigh presented with a pathologic fracture of the left proximal femur. A bone biopsy revealed a conventional high-grade osteoblastic osteosarcoma of the femoral diaphysis. In addition, Computed Tomography (CT) imaging showed a lesion on the left lamina of the fifth lumbar vertebra, L5.

During her follow-up, she developed hypercalcemia associated with hypophosphatemia. The serum Parathyroid Hormone (PTH) level was high at 802 pg/ml, confirming the diagnosis of PHPT. Based on clinical, biological, and radiological features, the diagnosis of a brown tumor of L5 was retained.

Based on the increasing number of clinical cases associating hyperparathyroidism and osteosarcoma, we present the hypothesis that chronically elevated serum PTH level, either by exogenous administration, which was already described in the literature, or via Primary Hyperparathyroidism, may have a carcinogenic effect.

Abbreviations

PHPT: Primary Hyperparathyroidism; PTH: Parathyroid Hormone; PO: Primary Osteosarcoma; FDA: Food Drug Administration

Introduction

Primary Hyperparathyroidism (PHPT) is a common endocrine disorder. It is responsible for a disturbance of the phosphorus-calcium metabolism. Hypercalcemia is the most frequent manifestation of PHPT, but it may also be revealed by its bone and renal complications [1]. It affects more women than men during the sixth decade of life [1]. In addition, PHPT has been associated, in a few rare cases, with PO [2,3].

It is a malignant bone tumor that is commonly seen in children and adolescents. The main sites of PO are the distal femur (40%), proximal tibia (16%), and proximal humerus (15%) [4]. Unusual sites of PO can lead to diagnostic difficulties because of the atypical clinical manifestations [4]. PTH controls both osteoblast and osteoclast activities. Its continuous overproduction in PHPT

increases osteoclastic bone resorption, but when administered intermittently, it increases bone mass by increasing the number and activity of osteoblasts [5]. Consequently, the last two decades have seen the use of PTH analogs as a treatment for osteoporosis in postmenopausal women. This has encouraged some studies to focus on the search for a possible carcinogenic effect of this substance [6].

PO is uncommon in patients with a history of PHPT. These cases lead us to speculate a causal relationship between the development of bone neoplasm and PHPT. We herein report a rare case of a patient who developed a PO associated with an ectopic parathyroid adenoma revealed by hypercalcemia.

Case Presentation

We report a case of a 40-year-old woman who presented a one-year history of low back pain and the recent onset of deep pain in her upper thigh. At first, the pain was treated with analgesics. Five months later, she had a left proximal femoral pathologic fracture caused by a lytic lesion. A bone biopsy was performed, concluding with a conventional high-grade osteoblastic osteosarcoma of the femoral diaphysis (Figure 1). As part of the extension assessment, Computed Tomography (CT) imaging did not reveal a secondary localization of the tumor. However, it showed a lesion on the left lamina of the fifth lumbar vertebra L5 without any sign of malignancy.

After bone surgery, she was referred to the carcinology department to receive multi-agent chemotherapy. During her follow-up, she presented high blood calcium levels. On biological results, her serum calcium level was 3,08 mmol/l, phosphorus level was 0.6 mmol/l. (Table). PHPT was suspected. Serum PTH level was high at 802 pg/ml, confirming the diagnosis of PHPT (Table). Based on clinical, biological, and radiological characteristics, the diagnosis of the brown tumor was retained.

A parathyroid Sestamibi Scintigraphy scan was performed, which showed an increased uptake at the upper left cervical area, suggesting an ectopic parathyroid adenoma (Figure 2). During her hospitalization, the patient received intravenous hydration combined with furosemide, with good outcomes on calcemia levels.

The patient underwent excision of the ectopic adenoma, with postoperative normalization of the blood calcium level. The anatomopathological examination confirmed the parathyroid nature of the mass. A 6-month follow-up showed no clinical or radiological signs of tumor recurrence, and her blood calcium level was within normal limits.

At the 1-year follow-up, the level of PTH was within a normal range (51 pg/mL), and the patient noticed a marked clinical improvement in lumbar pain with slight regression of the vertebral lesion on CT imaging.

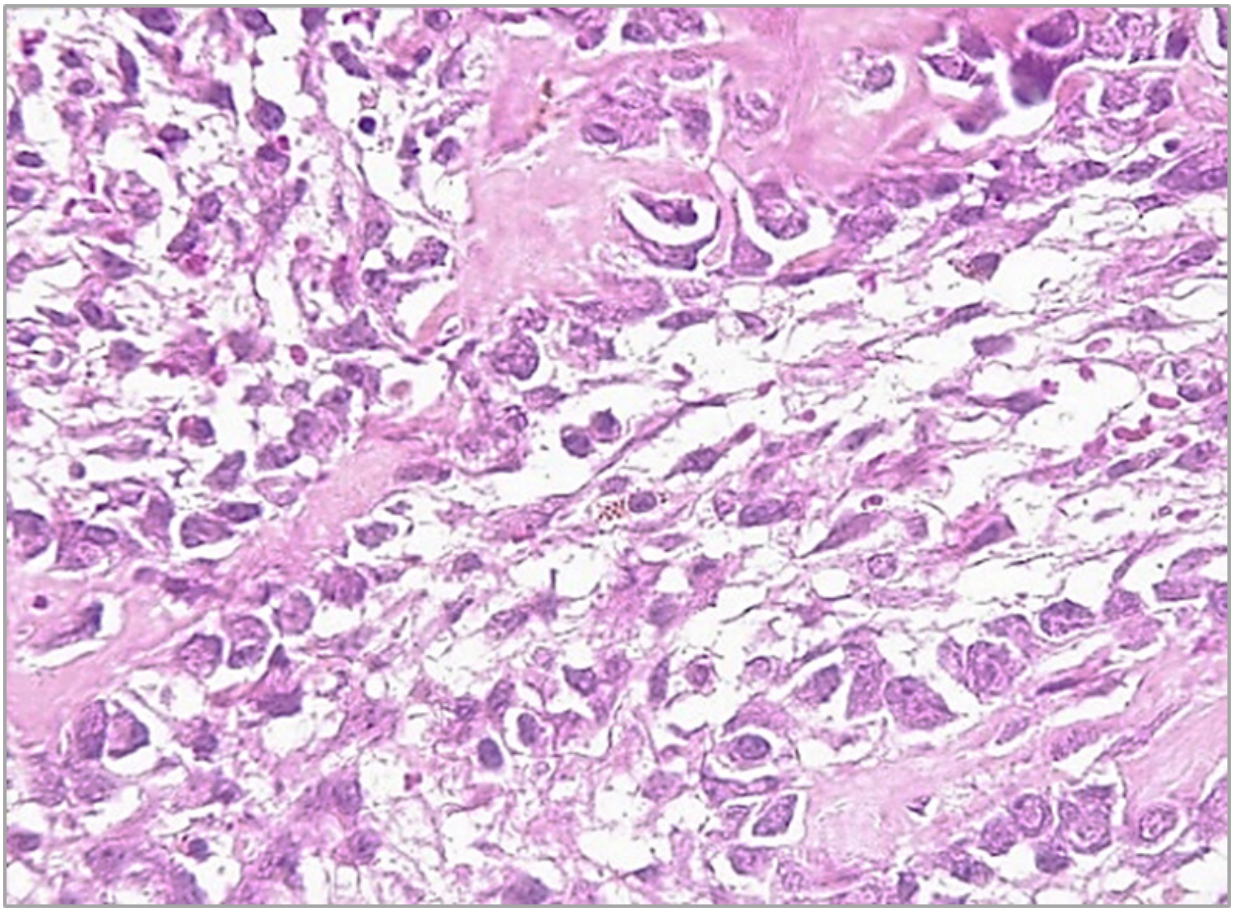

Figure 1: Micrograph showing a bone tumor composed of sarcomatous proliferation with osteoid formation (400x, H & E).

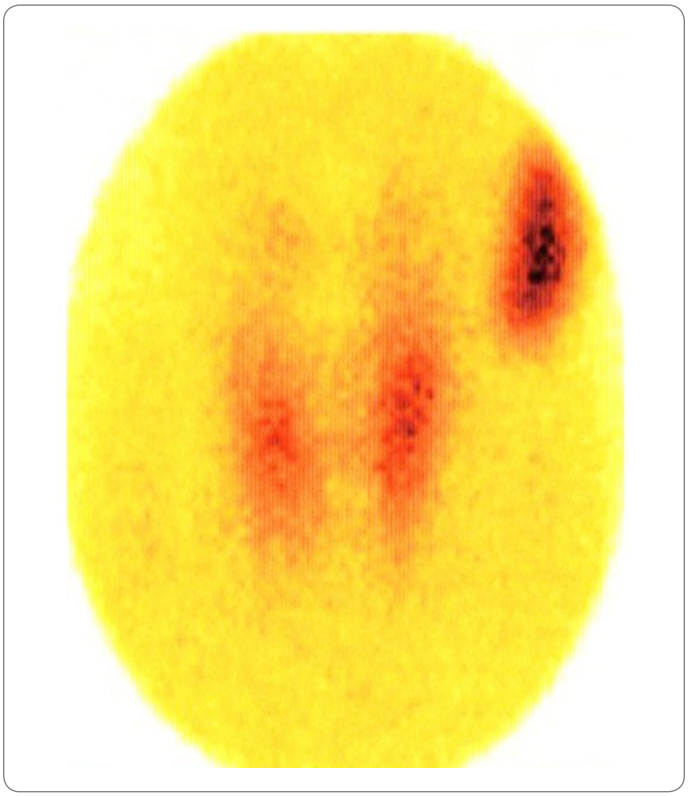

Figure 2: 99mTc-Sestamibi Scintigraphy scan shows uptake in both thyroid and parathyroid glands, with increased uptake at the upper left cervical area.

Discussion

Our case reports a rare association between a PO and PHPT. The main cause of PHPT is the development of an adenoma in a parathyroid gland which is responsible for the hypersecretion of PTH. Asymptomatic hypercalcemia detected by routine biochemical screening is the most common manifestation of PHPT but it can also be revealed by its urinary and bone complications [1]. In addition, biochemical studies have shown increased bone turnover with higher levels of bone formation markers [6]. PHPT is commonly seen in adult women [1].

The association of PO and PHPT is extremely rare. PO is the most frequent bone neoplasia in children [7]. In adults, it is less frequently observed and is often a malignant degeneration of a pre-existing bone disease [7]. The occurrence of osteosarcoma in our patient raises the hypothesis of a causal link between these two pathologies. The one-year history of low back pain and the presence of a brown tumor on imaging reflects the prolonged duration of PHPT and thus suggest chronic exposure to high serum PTH levels. To our knowledge, very few cases describe this rare association according to the literature [2], and our case is the first one that describes an ectopic localization of the parathyroid adenoma.

Among these cases, Spiro et al. have reported a case of a 34-year-old patient who was diagnosed with high-grade osteosarcoma of the mandible and PHPT, with a 2-month delay between these two diagnoses [2]. In addition, Mercuri et al. described a female patient who was simultaneously diagnosed with PHPT and a high-grade PO located in the proximal left tibia [2]. These two patients had a parathyroidectomy. The other reported cases described an association between a PHPT and malignant bone neoplasia with histological characteristics different from those of our patient [2]. This growing number of case reports has raised hypotheses about a probable carcinogenic effect of PTH. This has stirred controversy about the eventual side effects of prescribing PTH analogs as a treatment for osteoporosis in postmenopausal women [6].

Table: Biological characteristics.

	Result	Reference range
Calcium (mmol/l)	3.08	2.15–2.5
Phosphorus (mmol/l)	0.6	0.81–1.45
Magnesium (mmol/l)	1	0.73–1.06
Ca-U 24H (mmol/24H)	9	2.5–7.05
PTH (pg/ml)	802	10–65
Alkaline Phosphatase (U/l)	547	30–120

Ca-u: Urinary Calcium; PTH: Parathyroid Hormone.

To assess the possibility of a relationship between PO and PHPT, Jimenez et al. [8] conducted a study of a large cohort of osteosarcoma patients in which only three patients had this clinical association. This study concluded that PHPT is not more prevalent in patients with PO. Another study was carried out by Cinamon et al. [9] to evaluate the possibility of an association between elevated PTH and the development of bone neoplasia. This evaluation was required for the FDA approval of PTH administration as a treatment for osteoporosis. The final results found no association between PHPT and cancer [9].

In vitro studies have shown that PTH has a proliferative effect on osteosarcoma cell lines [10]. In fact, PTH selectively modifies the expression of the membrane, cytoskeletal and nucleoskeletal proteins of osteoblasts and osteosarcoma cells [10]. Furthermore, PTH induces stimulation of matrix metalloproteinase-13, known as collagenase-3, which is an enzyme linked to the invasiveness of various cancers, including breast and prostate cancer [11].

The 1-34 amino acid N-terminal fragment of PTH (Teriparatide) and human PTH (1-84) improve bone structure by promoting bone formation [12]. Some experimental studies have focused on the carcinogenic potential of these substances in Fisher 344 rats and have found that the incidence of bone neoplasms, particularly osteosarcoma, has increased [13].

A non-carcinogenic dose of teriparatide was established in a carcinogenicity study in Sprague Dawley rats, which showed the same result as the previous carcinogenic study [6].This incidence of osteosarcoma correlated positively with high doses and a prolonged duration of more than two years of treatment [6].

Cohort studies have not shown an association between these two situations, whereas other experimental studies have found an association between PTH and bone tumors, especially PO. Nevertheless, the FDA still authorizes the prescription of PTH analogs without insisting on the risk of prolonged prescription

of these molecules [14]. In November 2020, the American FDA removed the two-year lifetime treatment limitation and the warning regarding the potential risk of osteosarcoma from the PTH analog teriparatide [14]. But this is not the case for abaloparatide, a synthetic analogue of the PTH-related protein, the boxed warning for this molecule has not been removed. To our knowledge, the FDA is negotiating with the producer to remove this restriction [14].

Conclusion

Based on our case, experimental studies in rats, and *In vitro* studies, it seems that osteosarcoma may be related to chronic elevation of serum Parathyroid Hormone (PTH) levels in Primary Hyperparathyroidism (PHPT). Unlike our case, the early management of PHPT prevents prolonged exposure to elevated PTH levels. Since it takes years for carcinogenicity studies to be conclusive, it cannot be confirmed that elevated PTH serum level is free of carcinogenic properties. This hypothesis would raise questions about the decision to remove restrictions on using PTH analogs and their carcinogenic potential. Furthermore, this hypothesis highlights the importance of early diagnosis and managing PHPT through routine monitoring of phosphocalcic status.

Acknowledgments

The main writers of the manuscript are Dr. Nouira Sawsenand, Dr. Ach Taieb. All the authors participated in the revision of the review and helped in the patients' care.

Informed Consent: Oral and informed consent were obtained from the patient.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Informed consent was obtained for this publication.

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