PARATHYROID CARCINOMA REVEALED AFTER SURGERY FOR TERTIARY HYPERPARATHYROIDISM IN A HEMODIALYSIS PATIENT: A RARE CASE REPORT

CARCINOME PARATHYROÏDIEN RÉVÉLÉ APRÈS UNE INTERVENTION POUR HYPERPARATHYROÏDIE TERTIAIRE CHEZ UN PATIENT HÉMODIALYSÉ : PRÉSENTATION D'UN CAS RARE

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ABSTRACT

Parathyroid carcinoma is an exceptionally rare endocrine malignancy, accounting for less than 1% of primary hyperparathyroidism cases. Its occurrence in the setting of tertiary hyperparathyroidism secondary to chronic kidney disease is exceedingly uncommon and represents a diagnostic challenge. We report the case of a 37-year-old woman with end-stage renal disease on chronic hemodialysis and a history of hyperprolactinemia, who presented with diffuse bone pain associated with severe hypercalcemia and markedly elevated parathyroid hormone levels. Cervical ultrasonography revealed a left inferior parathyroid lesion measuring 19 × 19 mm. Technetium-99m sestamibi scintigraphy demonstrated pathological uptake corresponding to an orthotopic left inferior parathyroid gland.
Laboratory investigations showed a corrected serum calcium of 2.8 mmol/L and parathyroid hormone (PTH) level of 1203 pg/mL, leading to the diagnosis of tertiary hyperparathyroidism. The patient underwent subtotal parathyroidectomy with identification and dissection of the four pathological parathyroid glands. Intraoperatively, the right inferior gland was noted to be markedly adherent to surrounding tissues. A 7/8 subtotal parathyroidectomy was performed: the left superior, left inferior (carcinomatous), and right inferior (adherent) glands were resected in their entirety, and only half of the right superior gland was left in situ. Postoperative recovery was uneventful under antibiotics and analgesics, and the patient was discharged on postoperative day 3 after drain removal. Definitive histopathological examination revealed a left inferior parathyroid carcinoma, measuring 9 × 6 × 4 mm and weighing 3 g, with histological evidence of capsular invasion and infiltration of the adjacent fibro-adipose tissue, lymphatic invasion, and angioinvasion, associated with nodular hyperplasia of the remaining parathyroid glands. Postoperative laboratory assessment showed normalization of PTH levels to 24 pg/mL and correction of serum calcium to 1.95 mmol/L. Over 2 years of follow-up, PTH levels showed a progressive decline with no evidence of recurrence on serial cervical ultrasonography. Follow-up cervical ultrasonography demonstrated a normal thyroid gland without residual lesion. This case highlights the diagnostic difficulties of parathyroid carcinoma in the context of tertiary hyperparathyroidism and emphasizes the importance of histopathological examination for definitive diagnosis.
Keywords: Parathyroid carcinoma; tertiary hyperparathyroidism; hemodialysis; chronic kidney disease; subtotal parathyroidectomy; hypercalcemia.

RESUME

Le carcinome parathyroïdien est une tumeur maligne endocrinienne exceptionnellement rare, représentant moins de 1 % des cas d'hyperparathyroïdie primaire. Sa survenue dans le cadre d'une hyperparathyroïdie tertiaire secondaire à une maladie rénale chronique est extrêmement inhabituelle et constitue un véritable défi diagnostique. Nous rapportons le cas d'une femme de 37 ans présentant une insuffisance rénale terminale sous hémodialyse chronique et des antécédents d'hyperprolactinémie, qui s'est présentée avec des douleurs osseuses diffuses associées à une hypercalcémie sévère et un taux de parathormone considérablement élevé. L'échographie cervicale a mis en évidence une lésion parathyroïdienne inférieure gauche mesurant 19 × 19 mm. La scintigraphie au technétium-99m sestamibi a démontré une fixation pathologique correspondant à la glande parathyroïde inférieure gauche en position orthotopique. Le bilan biologique montrait une calcémie corrigée à 2,8 mmol/L et un taux de parathormone (PTH) à

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1203 pg/mL, conduisant au diagnostic d'hyperparathyroïdie tertiaire. La patiente a bénéficié d'une parathyroïdectomie subtotale avec identification et dissection des quatre glandes parathyroïdes pathologiques. En peropératoire, la glande inférieure droite présentait une adhérence marquée aux tissus environnants. Une parathyroïdectomie subtotale 7/8 a été réalisée : les glandes parathyroïdes supérieure gauche, inférieure gauche (carcinomateuse) et inférieure droite (adhérente) ont été réséquées en totalité, avec conservation de la moitié de la glande parathyroïde supérieure droite. Les suites opératoires ont été simples sous antibiotiques et antalgiques, et la patiente a été libérée au troisième jour postopératoire après ablation du drain. L'examen anatomopathologique définitif a révélé un carcinome parathyroïdien inférieur gauche, mesurant 9 × 6 × 4 mm et pesant 3 g, avec des signes histologiques d'invasion capsulaire et d'infiltration du tissu fibro-adipeux adjacent, d'invasion lymphatique et d'angio-invasion, associé à une hyperplasie nodulaire des glandes parathyroïdes restantes. Le bilan biologique postopératoire a montré une normalisation du taux de PTH à 24 pg/mL et une correction de la calcémie à 1,95 mmol/L. Sur un suivi de 2 ans, le taux de PTH a montré une décroissance progressive, sans récidive à l'échographie cervicale de contrôle. L'échographie cervicale de contrôle a objectivé une glande thyroïde normale sans lésion résiduelle. Ce cas souligne les difficultés diagnostiques du carcinome parathyroïdien dans le contexte d'une hyperparathyroïdie tertiaire et insiste sur l'importance de l'examen anatomopathologique pour le diagnostic de certitude.
Mots-clés : Carcinome parathyroïdien ; hyperparathyroïdie tertiaire ; hémodialyse ; maladie rénale chronique ; parathyroïdectomie subtotale ; hypercalcémie

INTRODUCTION

Parathyroid carcinoma is a rare endocrine malignancy accounting for less than 1% of all cases of hyperparathyroidism [1]. It is usually characterized by severe hypercalcemia and markedly elevated serum parathyroid hormone levels [1,2].

The occurrence of parathyroid carcinoma in the setting of secondary or tertiary hyperparathyroidism remains exceptionally uncommon [2,3]. Tertiary hyperparathyroidism develops in patients with longstanding secondary hyperparathyroidism, particularly those undergoing chronic hemodialysis, leading to autonomous secretion of parathyroid hormone and nodular hyperplasia of the parathyroid glands [4,5].

The diagnosis of parathyroid carcinoma in dialysis patients is particularly challenging because clinical, biological, and imaging findings frequently overlap with benign hyperplastic disease [1,3]. Imaging modalities such as cervical ultrasonography and technetium-99m sestamibi scintigraphy are useful for localization of pathological glands but do not reliably distinguish carcinoma from adenoma or hyperplasia [1,2].

We report a rare case of parathyroid carcinoma incidentally diagnosed after subtotal parathyroidectomy performed for tertiary hyperparathyroidism in a young woman undergoing chronic hemodialysis.

CASE PRESENTATION

A 37-year-old woman with a history of end-stage chronic kidney disease secondary to a congenital urinary tract malformation, on regular hemodialysis, and a history of hyperprolactinemia, was referred to our department for diffuse bone pain.

Laboratory investigations revealed hypercalcemia with a corrected serum calcium level of 2.8 mmol/L [AUTEURS : préciser calcémie totale/corrigée sur l'albumine/ionisée, et albuminémie] and markedly elevated parathyroid hormone levels reaching 1203 pg/mL.

Cervical ultrasonography demonstrated a left inferior parathyroid lesion measuring 19 × 19 mm. Technetium-99m sestamibi scintigraphy revealed findings suggestive of a pathological left inferior parathyroid gland in an orthotopic position.

Based on the clinical, biological, and radiological findings, the diagnosis of tertiary hyperparathyroidism secondary to chronic renal failure was retained.

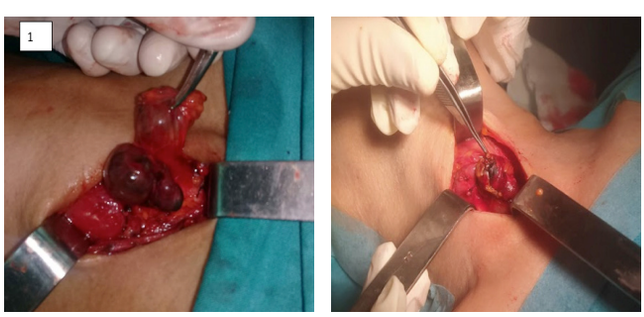
The patient underwent surgery under general anesthesia. Intraoperatively, all four parathyroid glands appeared enlarged and pathological (Figures 1 and 2). The right inferior parathyroid gland was noted to be highly adherent to surrounding tissues, without other macroscopic features suggestive of malignancy. A 7/8 subtotal parathyroidectomy was performed: the left superior, left inferior, and right inferior glands were resected in their entirety, and only half of the right superior gland was preserved in situ. The left inferior gland, subsequently found to harbor the carcinoma, was therefore removed in its entirety. No suspicious cervical lymph nodes were identified intraoperatively.

Postoperative management included analgesics and antibiotics. The postoperative course was uneventful. The cervical drain was removed, and the patient was discharged on postoperative day 3.

Definitive histopathological examination unexpectedly revealed a carcinoma of the left inferior parathyroid gland, whereas the right superior, left superior, and right inferior parathyroid glands showed only nodular hyperplasia. Notably, the carcinoma was identified in the left inferior gland, whereas it was the contralateral right inferior gland that had appeared markedly adherent intraoperatively; this discordance illustrates that intraoperative macroscopic features such as adherence are not reliable predictors of malignancy and underscores the necessity of systematic histopathological examination of all resected parathyroid tissue. Macroscopically, on gross pathological examination the tumor measured 9 × 6 × 4 mm, slightly smaller than the 19 × 19 mm lesion

estimated on preoperative cervical ultrasonography, a discrepancy commonly observed between imaging and gross measurements. The specimen weighed 3 g. Microscopically (Figures 3A–C), the tumor was composed of a proliferation arranged in cords and nests, with a slender, vascular stroma. Tumor cells had a rounded to ovoid, slightly hyperchromatic nucleus and eosinophilic, granular cytoplasm. Additional sections through the specimen demonstrated focal capsular breach with extension into the adjacent fibro-adipose tissue (Figure 3B) and a few vascular emboli (Figure 3C), together with lymphatic invasion (Figure 3A). Diagnostic criteria retained were these unequivocal invasive features (focal capsular breach, vascular and lymphatic invasion) rather than cytological atypia alone. No tumor necrosis was identified in the examined sections. Histological examination of the partially preserved right superior parathyroid gland showed normal parathyroid tissue. No lymph nodes were identified in the specimen, consistent with the absence of clinically or radiologically suspicious cervical adenopathy; consequently, no cervical lymph node dissection was performed. Surgical resection margins were free of tumor. Immunohistochemical staining for Ki-67 showed a low proliferation index. Parafibromin immunostaining showed retained expression, without loss of expression.

Postoperative laboratory evaluation showed normalization of PTH levels to 24 pg/mL with a corrected serum calcium level of 1.95 mmol/L. Follow-up cervical ultrasonography demonstrated a normal thyroid gland without residual lesion. The patient was followed for 2 years postoperatively, during which serum PTH levels showed a progressive decline and serial cervical ultrasonography showed no evidence of local recurrence.



Figures 1 and 2: Intraoperative appearance of the pathological parathyroid glands during subtotal parathyroidectomy

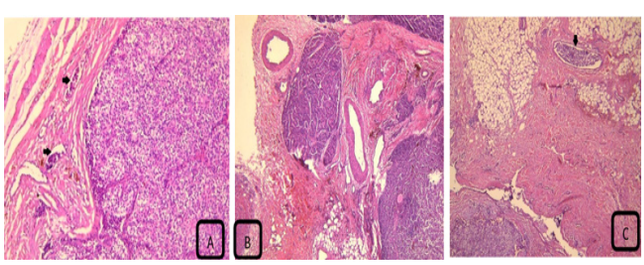


Fig A: Nodular parathyroid carcinoma predominantly composed of uniform chief cells with mild nuclear atypia (hematoxylin and eosin [H&E] stain, original magnification ×40). Lymphatic invasion is present at the tumor periphery (arrow).

Fig B: Tumor extension through the fibrous capsule with direct infiltration into the adjacent fibro-adipose tissue (H&E stain, original magnification ×40).

Fig C: Peritumoral angioinvasion (arrow) (H&E stain, original magnification ×40).

DISCUSSION

Parathyroid carcinoma remains an exceptionally rare malignancy, especially in patients with chronic kidney disease and tertiary hyperparathyroidism [1,2]. The pathophysiological mechanisms underlying malignant transformation in tertiary hyperparathyroidism remain poorly understood. Chronic stimulation of the parathyroid glands in dialysis patients may induce nodular hyperplasia and autonomous hormone secretion, potentially favoring neoplastic transformation [4,5].

Clinical presentation is frequently nonspecific. Several features have been proposed to raise suspicion for parathyroid carcinoma, including markedly elevated serum calcium, a very high PTH level, bone pain, a palpable cervical mass, a large tumor size, adherence to adjacent structures, and, when present, capsular or vascular invasion [1,6]. However, in patients with longstanding chronic kidney disease, multiglandular involvement and nodular hyperplasia are common confounding factors, as several of these features (severe hypercalcemia, markedly elevated PTH, bone pain) are also observed in advanced tertiary hyperparathyroidism without malignancy, which considerably limits their individual diagnostic value in this population [1,6].

Preoperative diagnosis remains difficult because imaging findings are not specific. Cervical ultrasonography and sestamibi scintigraphy are useful for localization but have limited value in differentiating malignant from benign lesions [1,2]. In our patient, the diagnosis of carcinoma was not suspected preoperatively despite markedly elevated PTH levels and hypercalcemia.

Intraoperatively, the right inferior parathyroid gland appeared highly adherent to adjacent tissues, a feature that may raise suspicion for malignancy. Notably, in our patient this adherent gland ultimately proved to be only nodular hyperplasia on histology, whereas the carcinoma was identified in the contralateral, macroscopically unremarkable left inferior gland. This discordance illustrates that intraoperative macroscopic findings, including adherence, are neither sensitive nor specific for malignancy, and that definitive diagnosis relies exclusively on histopathological examination [2]. Diagnosis should not rest on cytological atypia alone: the histological criteria retained as diagnostic of parathyroid carcinoma are unequivocal invasive

features, namely capsular invasion, vascular and/or lymphatic invasion, infiltration of surrounding tissues, and, in metastatic cases, nodal or distant spread; fibrous trabecular architecture and mitotic activity may support the diagnosis but are not sufficient in isolation [2,3].

Surgery remains the cornerstone of treatment and represents the only potentially curative therapeutic option [1,2]. Complete surgical excision with negative margins provides the best chance for long-term disease control [1]. In our case, the diagnosis of carcinoma was made only after subtotal parathyroidectomy, which raises the question of the adequacy of the initial surgical margins and of the need for further management. In our patient, the carcinomatous gland had been removed in its entirety during the initial subtotal parathyroidectomy, with histologically clean resection margins, and no suspicious lymph nodes were identified; the case was subsequently discussed with the oncology team, who concluded that complete surgical excision of the tumor was sufficient, without indication for completion neck dissection or adjuvant oncologic treatment. The postoperative evolution was nonetheless favorable, with normalization of serum PTH levels. Immunohistochemistry, particularly loss of parafibromin expression and a high Ki-67 proliferation index, has been proposed as an ancillary marker supporting the diagnosis of parathyroid carcinoma [2,3]. In our patient, Ki-67 immunostaining showed a low proliferation index, consistent with the generally indolent behavior of parathyroid carcinoma despite its locally invasive features, and parafibromin expression was retained. This illustrates that preserved parafibromin expression does not exclude the diagnosis of parathyroid carcinoma; the diagnosis in this case continued to rely primarily on unequivocal invasive histological features (capsular breach, vascular and lymphatic invasion) rather than on immunohistochemical findings alone.

Recent studies have highlighted the rarity of parathyroid carcinoma associated with renal hyperparathyroidism and emphasized the importance of close postoperative follow-up because of the high risk of recurrence and persistent disease [7,8]. Recently published case reports continue to underline the diagnostic difficulty of parathyroid carcinoma, describing vascular invasion and atypical mitoses as key histopathological clues to malignancy [10], as well as the potential severity of associated hypercalcemic crises, occasionally requiring dialysis to stabilize patients before definitive parathyroidectomy [9].

Our observation illustrates the diagnostic complexity of parathyroid carcinoma in hemodialysis patients and underlines the importance of systematic histopathological examination of all parathyroidectomy specimens obtained in the setting of tertiary hyperparathyroidism.

CONCLUSION

Parathyroid carcinoma associated with tertiary hyperparathyroidism is an extremely rare entity. Diagnosis is difficult before surgery because clinical and radiological findings frequently mimic benign hyperplastic disease. Histopathological examination remains essential for definitive diagnosis. Surgical treatment remains the cornerstone of management and should be followed by careful long-term surveillance.

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