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Metastatic Parathyroid Carcinoma: A Case Report

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Abstract **Case Report**

Parathyroid carcinoma is a rare clinical entity, characterized by its diagnostic difficulties. We report a case of a 58 year- old male who presented with a history of chronic hypercalcemia, the cervical ultrasound reported a deep left cervical mass, pushing back the left thyroid lobe and the trachea, oval in shape, with clear contours. The thoracic-abdominal-pelvic CT scan showed a left thyro ïd mass plunging into the posterior mediastinum with secondary bone lesions, the patient underwent a total thyroïdectomy with a diagnosis of parathyroid carcinoma on morphological and immunohistochemical studies, he was treated with first line chemotherapy with a good clinical and biological evolution. After the last course of chemotherapy, the patient presented bone pain resistant to analgesics with elevated hypercalcemia.

Keywords: Parathyroid carcinoma, metastasis, hypercalcemia, parathormone.

INTRODUCTION

Carcinoma of the parathyroid gland is rarely encountered in clinical practice representing 0.005% of all cancers. It represents only a small percentage of all head and neck neoplasms and is responsible for 0.4-5.2% of the causes of hyperparathyroidism [1]. This disease was first described in 1904 [2]. It should be suspected in the presence of a severe clinical and biological primary hyperparathyroidism syndrome, with very elevated serum calcium and parathyroid hormone levels [3]. The benign clinical presentation is partly responsible for the great diagnostic difficulty in distinguishing adenoma from parathyroid cancer [4]. Surgery is crucial, since oncological removal is the only potentially curative treatment, and the place of adjuvant treatment has yet to be established [5]. Through this observation, we will develop the main clinical, histological and therapeutic characteristics of this clinical entity.

CASE REPORT

We report a case of a 58 –year- old male, already followed for hyperthyroidism with poor compliance to treatment, who was referred to our training by the rheumatology department where he was hospitalized for multiple iterative fractures, in a picture of acute hypercalcemia. The history of his illness was 7 months before, when he presented an asthenia, diffuse bone pain, polyuric polydypsia syndrome and constipation, all evolving in a context of altered general condition. The physical examination showed a patient in a wheelchair, with total functional impotence of both lower limbs, associated with a painless left latero-cervical mass of hard consistency measuring 4cm in diameter. The cervical ultrasound reported a deep left cervical mass, pushing back the left thyroid lobe and the trachea, oval in shape, with clear contours, measuring 4*3, 8*5,7cm, with heterogeneous tissue structure. The preoperative biological workup showed hypercalcemia at 159 mg/L, parathormone at 925.8 pg/mL. The thoracic-abdominal-pelvic CT scan showed a left thyroid mass plunging into the posterior mediastinum with secondary bone lesions. At the end of this assessment, a surgical treatment was indicated, the surgical procedure consisted in the removal of the mass. Malignancy suspected, the surgical procedure was completed by a total thyroidectomy and a lymph node curage of the homolateral recurrent chain. The specimen was sent for histological study, which described on the total thyroidectomy specimen: endocrinoid tumor proliferation whose morphological aspect does not allow to eliminate a parathyroid origin, associated with a diffuse basedowified goiter (Figure 1). At lymph node level: non-specific reactive adenitis (7N-/7N). The immunohistochemical study of the specimen showed an aspect suggestive of a parathyroid carcinoma (Figure 2 and 3).

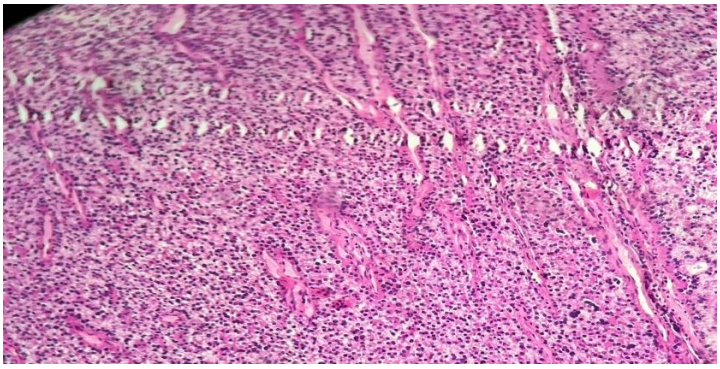

Figure 1: Parathyroid carcinoma cells proliferation HE*40

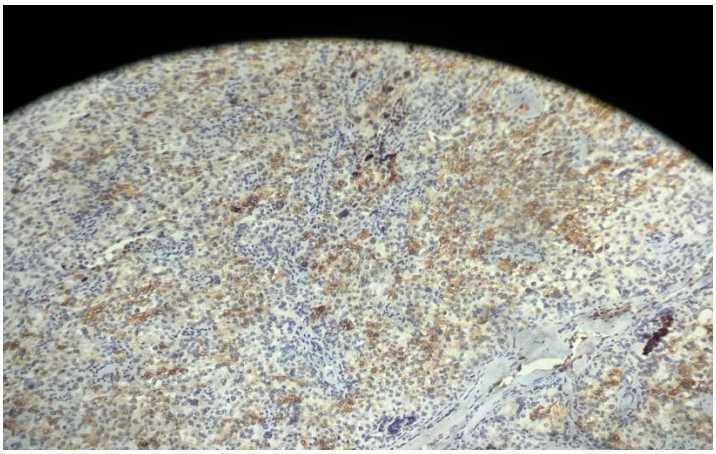

Figure 2: Ac anti-chromogranine A HE*40

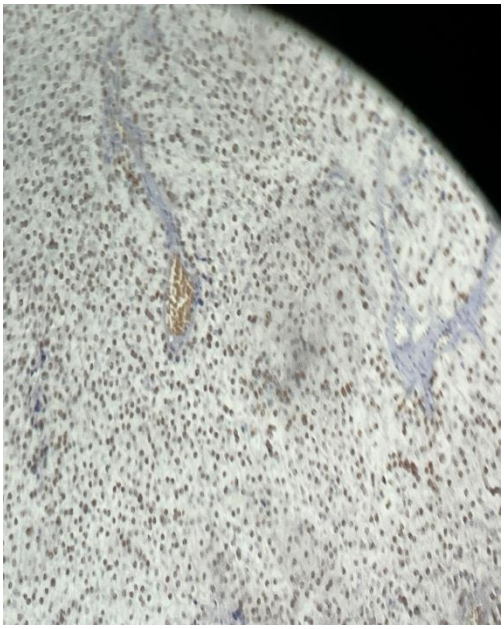

Figure 3: Positivité nucléaire des cellules tumorales HE*40

The postoperative course was simple and marked by a decrease in the levels of calcemia to 83 mg/L, and parathormonemia to 3pg/ml. Three months after surgery, the patient received first-line chemotherapy of the Endoxan type, given the metastatic status of the tumour, at a dose of 160mg/d every 3 weeks, for 12 cycles. A thoracic-abdominal-pelvic CT evaluation at C5 described persistence of secondary bone lesions, and the appearance of bilateral obstructive renal calculi on the right side, the level of calcemia and parathormonemia was stable. After the last course of Endoxan, the patient presented to the emergency room with disabling diffuse bone pain, and was put on a level III analgesic treatment. The assessment after the end of chemotherapy by thoraco-abdomino-pelvic CT revealed the appearance of retroperitoneal adenopathies, with

significant right hydronephrosis upstream of a corraliform stone, associated with diffuse mixed bone involvement, vertebral, costal, sternal and right scapular, as well as bilateral sacral and iliac lytic involvement, with elevation of the calcemia level to 135.14 mg/l and of the TSH level to 209.12Mu/l, corrected by hydration at 3L/day with administration of Lasilix 40mg * 2 /day in IV and corticosteroid therapy 60mg /day for 7 days.

DISCUSSION

Our case report deals with the diagnostic and therapeutic problems that arise when hyperparathyroidism is discovered. The main etiologies are parathyroid adenomas, parathyroid hyperplasia and parathyroid cancer. The latter is an exceptional cause of primary hyperparathyroidism, responsible for only 0.1-5% of primary hyperparathyroidism [6]. It is a very rare malignant tumor with an estimated prevalence of 0.005% of all cancers [7, 8]. Its preoperative diagnosis is difficult [6]. Because of its poor prognosis, differentiating PC from other benign parathyroid tumors is a real challenge [9]. The age of onset is between 45 and 59 years. There is no female preponderance as in parathyroid adenomas [4]. The etiopathogenesis remains unknown, but it seems that certain genetic and environmental factors interact in a very complex way. Irradiation of the neck especially at a young age increases the risk of parathyroid neoplasia [10, 11]. Some genetic mutations have been reported in parathyroid carcinoma, which mainly concern oncogenes, tumor suppressor genes: losses of 1p, 4q, and 13q, gains of 1q, 9q, 16p and Xq have been frequently observed in parathyroid carcinoma [12]. Other studies have implicated cyclin D1 overexpression in the genesis of parathyroid carcinoma as it has been identified in 91% of these tumors [13]. A strong association has been found between parathyroid carcinoma and the 'hyperparathyroidism jaw tumor' syndrome which is a rare autosomal dominant disease where affected individuals develop primary hyperparathyroidism, mandibular fibroosseous tumors, renal and/or uterine tumors [14]. Parathyroid carcinoma is a rare malignancy that usually shows nonspecific symptoms associated with hypercalcemia. These are weakness, bone pain, fatigue, nervousness, depression, weight loss, anorexia, nausea, vomiting, thirst, abdominal discomfort, and palpitations. The clinical picture that carcinoma of the parathyroid gland gives is the same as that of hyperparathyroidism due to adenoma. Patients with parathyroid carcinoma have a greater incidence of renal and bone disease compared with patients with benign hyperparathyroidism [15]. About 70% of patients have skeletal disease, which is usually manifested as osteoporosis or ostitis fibrosa cystica/brown tumor [16]. About 30% of patients have renal disease, which is manifested as nephrolithiasis, polyuria, or polydypsia. About 15% of patients have pancreatitis [16]. About 50% of the patients have a palpable cervical mass. The other physical findings are hypertension or, in rare cases, vocal cord paralysis. Some signs are never usual in benign hyperparathyroidism and should draw attention such as dysphonia (pointing to recurrent paralysis due to local nerve invasion), as well as dysphagia, which are highly suspicious of malignancy [17], and about 33% of patients have distant pulmonary, hepatic and bone metastases [18]. The patients are usually markedly hypercalcemic and usually hypophosphatemic. Serum calcium levels are 3.5 mmol/l or higher. The serum parathormone level is generally increased usually more than five times the normal. The serum alkaline phosphatase level is mildly elevated; serum creatinine and erythrocyte sedimentation rate are elevated, too. Patients usually have anemia [1] and elevated alkaline phosphatase, hypophosphatemia and hyperchloremic metabolic acidosis are often found [11]. In front of these clinico-biological signs of primary hyperparathyroidism, preoperative imaging should systematically include a cervical ultrasound, as parathyroid cancer appears on ultrasound as a hypoechoic lobulated lesion with irregular boundaries. A recent retrospective study has specified some ultrasound criteria predictive of malignancy such as the presence of intra-lesional calcifications and infiltration of surrounding tissues. On the other hand, the absence of intra-tumoral vascularization, the ovoid shape of the lesion with a thick capsule have a negative predictive value, which make malignancy unlikely [1, 17]. Studies have shown that the ultrasound sensitivity for parathyroid carcinomas varies from 50 to 90% [17]. This ultrasound will be completed by a Tc99m-sestamibi scan, which is 91% sensitive, and which allows the presence of a parathyroid tumor to be demonstrated (hyperfixation) and localized [19]. These two reference examinations confirm the parathyroid nature of the cervical mass and look for the presence of any cervical adenopathy. In case of strong presumption of malignancy, a cervical MRI can study the locoregional extension and demonstrate a cervical mass in T1 and T2 hypersignal, multi-centimetric at the level of the posterior face of the thyroid. A thoraco-abdomino-pelvic CT scan will look for distant metastases [20]. There is no TNM classification because of the rarity of this disease. Therefore, only the histological study allows a definite diagnosis of parathyroid carcinoma. Fine needle aspiration should be avoided because, in addition to the difficulty of confirming the malignant nature of cytological samples, it may cause tumor dissemination. However, it can be useful to differentiate between tumor recurrence and fibrosis [18]. Intraoperative diagnosis of parathyroid carcinoma is not easy. Macroscopically it is a solid mass, hard consistency, polylobed, encapsulated, gray to whitish, measuring more than 3cm in diameter, weighing more than 12g and adhering closely to the thyroid lobe or adjacent tissues (subhyoid muscles, recurrent nerve, trachea, esophagus,...). Microscopically, Schantz and Castelman have defined criteria for the diagnosis of parathyroid carcinoma,

which are: the presence of mitosis figures, trabecular or rosette architecture, the presence of fibrous bands radiating from the capsule, capsular invasion and vascular emboli [21]. Unfortunately, none of these features is diagnostic of parathyroid carcinoma. Some of them can be found in parathyroid adenomas [16]. However, the presence of more than two of the abovementioned criteria makes the diagnosis of carcinoma highly probable [22] . Recently, immunohistochemistry techniques using monoclonal antibodies, PCNA and Ki67, have been studied and can be used as a prognostic factor of aggressiveness. In our patient, we observed a tumor proliferation made of cohesive clusters of endocrine appearance, the tumor cells are of medium size with regular nuclei. The adjacent thyroid parenchyma is of lobular architecture with septa containing numerous lymphoid follicles. Prior to any treatment, medical preparation is necessary to control the metabolic emergency (hypercalcemic crisis) and consists of massive intravenous rehydration with isotonic saline and administration of loop diuretics. Biphosphonates, which block bone resorption, may be associated. Sometimes hemodialysis sessions to restore blood calcium levels may be necessary [18]. Surgical resection is the basic treatment for parathyroid carcinoma [4, 11]. Cervical lymph node metastases are found in about 25% of patients [11]. The surgical procedure should include removal of the parathyroid tumor, the homolateral thyroid lobe, and the pretracheal and recurrent lymph nodes [2]. Homolateral jugulocarotid dissection is performed if there are obviously metastatic adenopathies. Most authors agree that an incomplete resection is at high risk of recurrence and that an enlarged tumor removal is the best option to hope for cure [1, 4, 11]. It is imperative not to rupture the parathyroid capsule during surgical excision to avoid seeding of tumor cells and local recurrence. Sacrifice of the inferior laryngeal (recurrent) nerve is only necessary if it is macroscopically invaded [23]. In our case, a capsular rupture was noted after removal of the mass. The parathyroid carcinoma is radioresistant. There is no predefined radiotherapy protocol. However, for some authors, postoperative external radiotherapy with a dose of 40 to 70 Gy can be proposed in case of locoregional invasion and it seems to reduce the risk of local recurrence [18, 24]. Chemotherapy is generally ineffective in the treatment of parathyroid carcinoma and many drugs have been used such as dacarbazine, vincristine, actinomycin D and adriamycin, either alone or in combination with 5-fluorouracil and cyclophosphamide [18]. Chemotherapy, for which protocols are not yet established, can only be conceived for poly metastatic tumors. Radiotherapy and chemotherapy can be proposed as palliative treatment for patients with inoperable or metastatic parathyroid carcinoma, as in our case [21]. Morbidity and mortality in parathyroid cancer are mainly related to PTH hypersecretion and the resulting hypercalcemia, rather than to the tumor extension itself. Thus, management of hypercalcemia is imperative in patients with unresectable local tumor or generalized metastases [4]. The risk of local and metastatic (pulmonary, bone, and liver) recurrence has been estimated to be 25-60% within 2-5 years after initial resection [10, 22]. Most recurrences occur within the first 3 years, but recurrences beyond 20 years have also been reported, hence the usefulness of prolonged surveillance [10, 15]. The overall survival at 5 years is 85% and at 10 years is 49-77% [19].

CONCLUSION

Parathyroid carcinoma is a rare hypersecretory malignant tumor whose diagnosis remains difficult. It is suspected in the presence of a severe primary hyperparathyroidism syndrome and then by the appearance of the tumor gland during surgery and its extension to adjacent tissues. The diagnosis is confirmed by histological study using recent immunohistochemistry techniques. The treatment of choice is surgical and is associated with external radiotherapy in some advanced cases. Chemotherapy has not yet proven to be effective. Post-treatment monitoring is based on the determination of blood calcium and parathyroid hormone levels. Patient survival depends on an aggressive surgical approach to the primary lesion and recurrent disease. The death is usually due to long-term effects of hypercalcemia and the overall survival at 5 years is 85% and at 10 years is 49-77%.

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