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Delayed diagnosis of parathyroid cancer manifested with pubic bone lesions and chronic kidney failure.

Tricks and pitfalls of management

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Delayed diagnosis of parathyroid cancer manifested with pubic bone lesions and chronic kidney failure. Tricks and pitfalls of management

INTRODUCTION: *Parathyroid cancer (PTC) is an extremely rare malignancy with an incidence of 5.7 per 10 million people. The exact preoperative or intraoperative diagnosis is difficult, but of paramount importance, because resection with negative margins is the only effective treatment.*
CASE REPORT: *A 46-years-old female was referred from another hospital with a diagnosis of "hyper-functioning thyroid nodule", based on the ultrasound showing a lesion of the right thyroid lobe and elevated FT4. At the admission, she had severe pain in the right inguinal area, fatigue, muscle weakness, and excessive diuresis.*
The blood assay demonstrated serum calcium of 4.02 mmol/l, parathyroid hormone of 1433.2 pg/ml, FT4 of 17.49 pmol/l, creatinine of 296 µmol/l. CT showed a tumor of the right thyroid lobe with a size of 2.5. A right lobectomy was performed. Right parathyroid glands were not found. Because of the constellation for hyperparathyroidism and suspicion of parathyroid malignancy ipsilateral and central lymph node dissection and partial removal of the right sternothyroid muscle were performed, which correlated with a significant intraoperative drop in the parathyroid hormone. Three months later, a re-resection was performed because of SPECT-CT evidence for residual parathyroid tissue.
CONCLUSION: *The timely diagnosis of PTC is a prerequisite for a good outcome. The best preoperative indicators are serum parathyroid hormone > 4 times above the upper limit, serum calcium > 14 mg/dL, a palpable neck mass, and a local invasion found intraoperatively. The only curative treatment is the complete removal of the tumor with a negative margin.*

KEY WORDS: Delayed diagnosis, Hyperparathyroidism, Parathyroid cancer, Surgery

Introduction

Parathyroid cancer (PTC) is extremely rare accounting for less than 1% of all parathyroid disorders.[1, 2] The incidence is estimated to be 5.7 per 10 million people.[1]

Primary hyperparathyroidism (PHP) is the most common manifestation (90%). The preoperative diagnosis of PTC is extremely difficult (impossible in up to 75-100%) but remains of paramount importance because resection with negative margins is the only effective treatment.[2-4] The fresh-frozen examination is not reliable for differentiation between adenoma and cancer so the diagnosis should be based on a high index of clinical suspicion and intraoperative findings.[5]
Herein, we present a case of delayed diagnosis of PTC manifested with pubic bone lesion and chronic kidney failure and discuss the possible pitfalls and errors.

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Case report

A 46-years-old female was referred from another hospital with a diagnosis of "hyper-functioning thyroid nodule", based on the ultrasound showing a lesion of the right thyroid lobe and elevated FT4. At the admission, she had severe pain in the right inguinal area, fatigue, muscle weakness with significantly restricted movements, and excessive diuresis. The physical examination revealed a palpable mass with a visible deformation of the neck and significant pain in the right inguinal area. The blood assay demonstrated serum calcium of 4.02 mmol/l, parathyroid hormone of 1433.2 pg/ml, FT4 of 17.49 pmol/l, TSH of 0.377 μIU/ml, and creatinine level of 296 μmol/l. The native body CT finding was interpreted as a well-demarcated mass of the right thyroid lobe with a size of 35 mm and a lesion of the right superior pubic bone (Figs. 1, 2). A contrast was refused because of the high level of creatinine. The bone biopsy demonstrated osteitis fibrosa cystica (brown tumor), which correlated with the laboratory constellation for hyperparathyroidism (Fig. 3).

Despite the interpretation of the radiologist, the patient was scheduled for operation with suspicion of PTC. Intraoperatively, a well-demarcated tumor of the right thyroid lobe with a size of 2.5x1.5x1.5 cm was found. A right lobectomy was performed (Fig. 4). The fresh-frozen examination was indicative of malignancy. Right parathyroid glands were not found. To be sure that they were removed completely, an ipsilateral lymph node dissection and partial removal of the right sternothyroid muscle in contact with the tumor were performed.

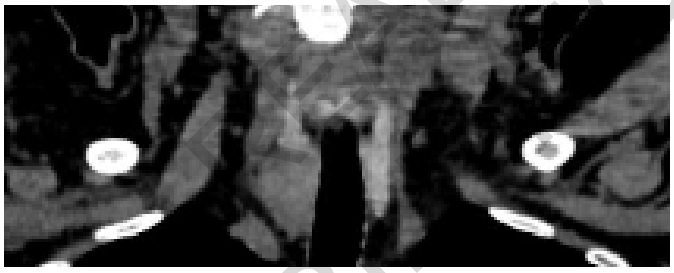

Fig. 1: A native CT – a well-demarcated mass with a diameter of 35 mm located at the lower pole of the right thyroid lobe.

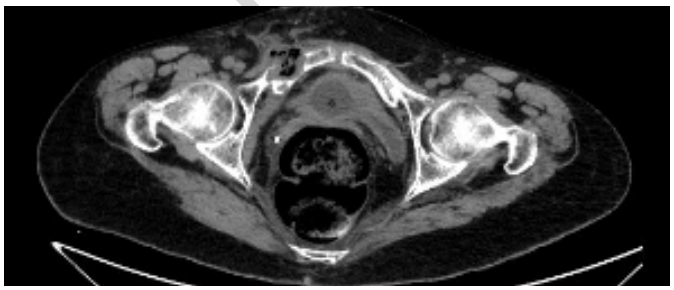

Fig. 2: A native CT – a lesion with fracture of the right pubic bone.

The intraoperative blood assay of the parathyroid hormone level revealed a drop from 1433.2 pg/ml to 186.4 pg/ml, which confirmed that the parathyroid tumors were removed. The histopathology demonstrated PTC infiltrating the thyroid gland (T2N0) (Figs. 5, 6).

There was a slight temporary vocal cord paralysis, which completely resolved after three months and complete normalization of the serum calcium and PTH to reference values. Due to mutation in exon 5 (p.Arg126*) of the CDC73 gene a familial screening was performed, but no CDC73-associated diseases in the relatives were found. Three months later, because of an increase in the PTH, a SPECT-CT with 99mTc was performed. It demon-

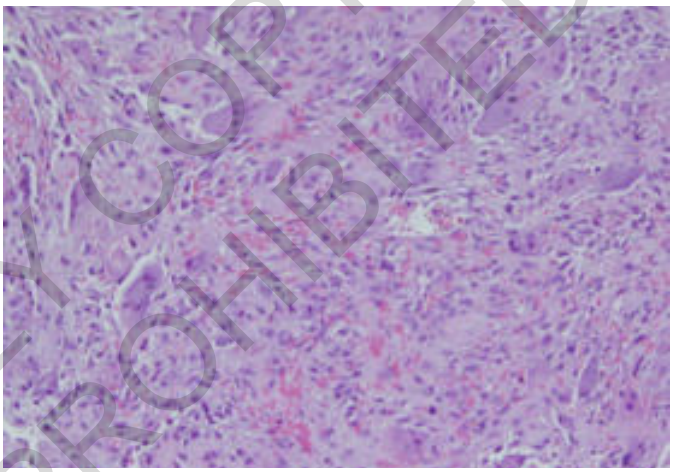

Fig. 3: A microscopic view of the pubic bone biopsy compatible with osteitis fibrosa cystica (HE, 10 x).

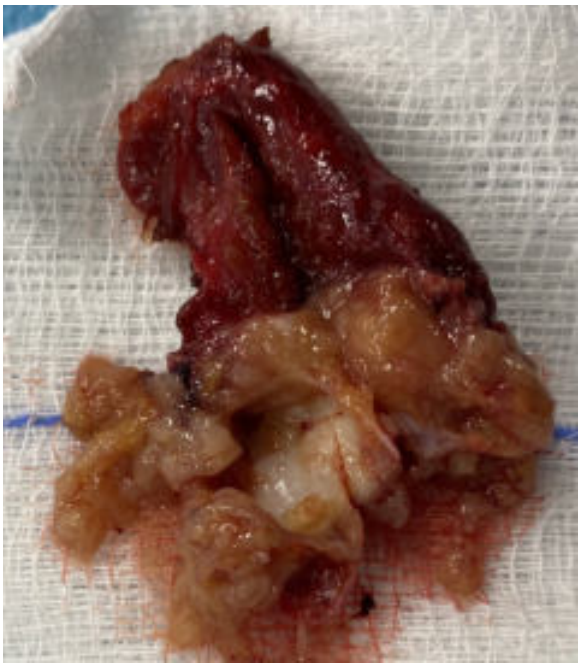

Fig. 4: The specimen of the right thyroid lobe with a yellowish mass infiltrating its lower pole.

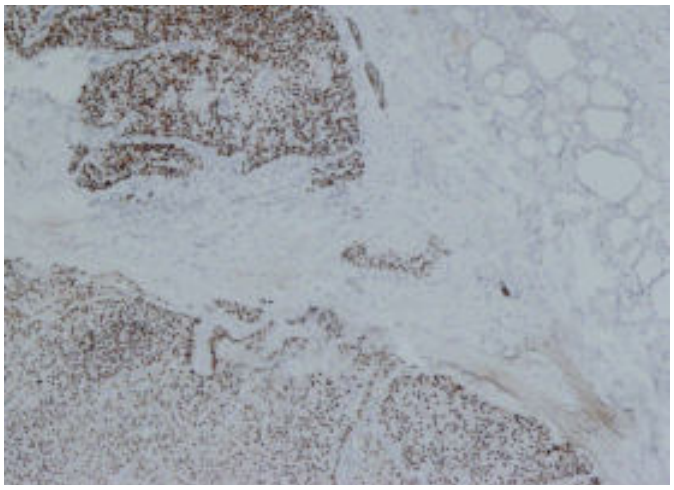

Fig. 5: A microscopic view – GATA-positive parathyroid cancer (4 x).

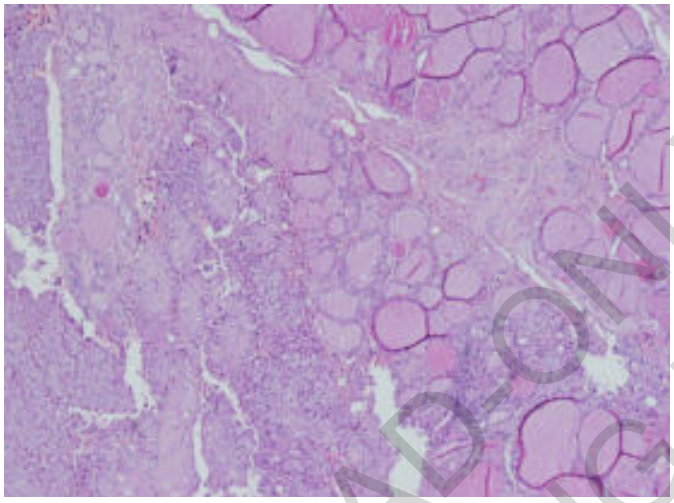

Fig. 6: A microscopic view – infiltration of the thyroid gland (HE, 4 x).

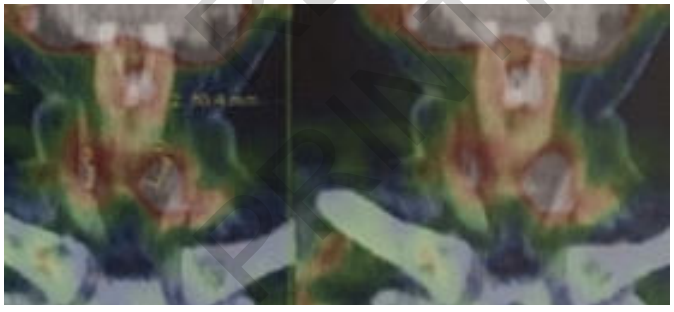

Fig. 7: SPECT-CT – a small parathyroid tissue at the site of the previous operation with SUV 5.6 and a diameter of 6.8 mm, and a single enlarged parathyroid gland contralaterally with a diameter of 7.2 mm and SUV 14.6.

strated a small parathyroid tissue with a diameter of 6.8 mm and SUV 5.6 at the site of the previous operation, and a single enlarged parathyroid gland contralaterally with a diameter of 7.2 mm and SUV 14.6 (Fig. 7).

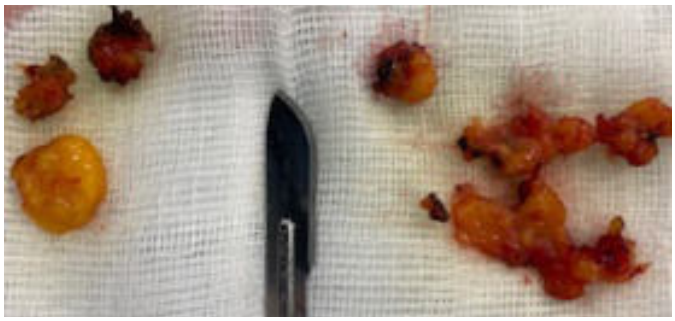

Fig. 8: The specimen after the second operation.

Re-resection without complications was performed (Fig. 8). The histology did not reveal malignancy. There was an uneventful recovery with complete normalization of the PTH.

Discussion

Rare diseases are frequently associated with delayed diagnosis. The early diagnosis of PTC before the development of metastases or organ failure is the main factor determining survival and quality of life. The preoperative diagnosis is a prerequisite for radical surgery but is frequently impossible (75-100%)[3,4]. Very frequently, PTC is not diagnosed preoperatively, which warrants the search for reliable markers. The only comparative series of Quaglino et al. reported the presence of symptoms in 91% of the PTC vs. 44% in benign PHP at the time of diagnosis [6]. In contrast to PHP, the patients with PTC are younger, with serum calcium > 14 mg/dL, serum parathyroid hormone > 4 x above the upper limit, and a palpable neck mass of 70% similar to the presented case [3-9]. Primary adenomas are rarely large, whereas PTC is usually 3 cm or larger. Due to the excessive PTH and serum calcium, the symptoms of PTC are more pronounced than in PHP (91% vs. 44%) [6]. Most cases manifest with fatigue, muscle weakness, loss of bone density, excessive diuresis, and kidney failure [10]. A recent series from Indonesia reported skeletal involvement in 50% of the cases [4].

Benign adenomas exist in 21% either before or concurrent with PTC, as in our case [7]. The clinicians, however, should be aware that 10% percent of the PTCs are nonfunctioning and the only indicative symptom is a neck mass [5].

Ultrasound is a useful initial screening method. The larger size, heterogeneous texture, irregular shape, and local invasion are suggestive of PTC [11]. MRI is useful for the assessment of the local invasion, whereas CT has a limited role [7]. SPECT-CT with 99mTc allows localization of the parathyroid tissue in 90% of the cases and is also useful for the detection of recurrent disease and distant spread of PTC (Fig. 7) [12,13]. The combination with ultra-

sound has an overall sensitivity of 95% and an accuracy of 91% [12].

The timely recognition of the malignancy during the operation remains the most important factor for adequate treatment. The fresh-frozen examination is not reliable for differentiation between adenoma and cancer, although some authors reported an exact diagnosis of 67% [2,10]. The complete removal of the tumor with a negative margin carries 85% overall survival and 5- and 10-year survival of 90% and 67%, respectively [7]. The removal of the ipsilateral thyroid lobe in absence of invasion does not improve the prognosis; the contralateral neck inspection is not recommended [5]. The incomplete resection is associated with a 13-fold higher risk for recurrence (0% vs. 55%) [6]. They are best treated by repeated surgery. The overall rate of unilateral or bilateral vocal cord paralysis over the patient's life is 38% [5]. In the presented case there was temporary vocal cord paralysis after the first operation, which resolved completely after three months. The second operation was free of complications despite the bilateral neck dissection.

Our patient had a mutation in exon 5 (p.Arg126*) of the CDC73 gene, which has been reported in 67% of sporadic parathyroid cancers [14]. It is associated with jaw tumors (ossifying fibromas), hyperparathyroidism, renal cysts, and PTC, which warrants familial screening for these conditions. In contrast, none of the cases in the series of Quaglino et al. had such mutation [3,6].

We think that to some extent the mismanagement of the presented case is educational.

First of all, there was a misinterpretation by the radiologist of the right neck mass (interpreted as a thyroid tumor) and an omission of the left parathyroid hyperplasia. Initially, during the exploration, we were also misled that the tumor originated from the thyroid gland. Last but not least, if the SPECT-CT was performed at the index admission it probably would prevent the second intervention. The radiologists refused to perform a contrast CT and SPECT because of the institutional protocol for avoiding contrast in case of a high serum creatinine level. Due to a lack of experience, there was no correct interpretation of clinical and laboratory findings in the presented case. Because of the suspicion of PTC, we performed an intraoperative assay of PTH to confirm that the tumor was removed.

Conclusion

The timely diagnosis of PTC is a prerequisite for a good outcome. The correct interpretation of clinical and laboratory findings is the most important determinant of the correct diagnosis. The best preoperative indicators are serum parathyroid hormone > 4 times above the upper limit, serum calcium > 14 mg/dL, a palpable neck mass, and a local invasion found intraoperatively. SPECT-CT with 99mTc allows precise localization of the parathyroid tissue in 90% of the cases. The only curative treatment is the complete removal of the tumor with a negative margin.

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