

# A review of parathyroid mass and patients with nonspecific complaints

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## Abstract

In this review, parathyroid mass and its nonspecific symptoms are discussed. In daily clinical practice, patients present with varying symptoms, including depression, chest pain, pancreatitis, or nonspecific fatigue. If the patient is not tested for a parathyroid mass along with performing routine electrolyte tests, diagnosing such a patient with a parathyroid mass may take several years. This issue and situation are discussed in this review.

## Keywords

Parathyroid, nonspecific complaints, carcinoma, endocrine disorder, hyperparathyroid, symptoms

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## Introduction

Parathyroid carcinomas are very rare endocrine conditions. They account for less than 1% of all primary hyperparathyroid conditions. Parathyroid masses are either asymptomatic and they are discovered incidentally or they are detected by a wide spectrum of symptoms, which are nonspecific and vary widely, ranging from fatigue to depression and pancreatitis to chest pain. Patients may attend the hospital with a hypercalcemic crisis.<sup>1</sup> Clinicians should suspect parathyroid masses and perform imaging tests such as simple biochemical electrolytes, especially Ca, and ultrasound (USG).

In this review, we report eight cases on this topic.

## History

Sir Richard Owen identified the parathyroid glands for the first time. He described

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the parathyroid glands as yellow, dense bodies when he conducted a study on *Rhinoceros unicornis* in a museum in England.<sup>2</sup>

Later, in 1880, a medical student in Sweden showed the parathyroid glands in animals, such as cats, rabbits, and horses. They were also identified in humans and named the glandula parathyroidea.<sup>2,3</sup>

Between 1857 and 1930, when the French physiologist Gley removed these glands during a thyroidectomy, tetanus was observed to develop. It was understood that the parathyroid glands were very important for the continuity of life.<sup>4</sup> It was shown by Collip that the hormone secreted by these glands controls blood calcium levels.<sup>5</sup>

In 1959, Rasmussen and Gravy succeeded in purifying parathyroid hormones.<sup>6</sup>

## Embryology

Superior parathyroid glands consist of the pharyngeal pouch endoderm and migrate to the thyroid gland. Inferior parathyroid glands develop from the endoderm of the pharyngeal pouch. They migrate with the thymus. Sometimes, they are located in the mediastinum by continuing downward with the thymus or staying closer to the thyroid. This explains the different locations of the parathyroid masses.<sup>7</sup>

## Anatomy

There are usually four parathyroid glands that are yellow and weigh 35–40 mg. Their length is 2–7 mm, width is 2–4 mm, and the thickness is 2–5 mm. They are soft glands surrounded by a fibrous capsule, but their number and location can be variable. From the pharynx to the mediastinum, it may be ectopic in a very large area. Blood supply to the upper parathyroid glands is from the superior thyroid artery, while that of the lower parathyroid glands is from the

inferior thyroid artery.<sup>7,8</sup> Venous drainage also occurs in the superior, middle, and inferior thyroid venules. However, lymphatic drainage occurs in the pretracheal, prelaryngeal, and jugulodigastric lymph nodes.

## Physiology

Chief cells make up most of the parathyroid gland. They regulate the normal calcium level in the blood.<sup>9</sup> While models such as sympathectomy, vagus stimulation, ovariectomy, calcium injection, propranolol intake, and streptozotocin inhibit parathyroid hormone (PTH) release from these cells, a low calcium diet, vagotomy, calcitonin, isoproterenol, and estrogen increase the hormone production.

The second cell type is oxyphil cells. These cells are found among chief cells. They are cells with a large cytoplasm and they have more energy than mitochondria. These cells secrete vitamin D 1 $\alpha$  OHase and the parathormone related peptide (PTHrP), calcitriol.<sup>10,11</sup>

Another type of cell is the water clear cell consisting of a vacuolated cytoplasm. They are usually found in small numbers, but in cases such as hyperplasia or parathyroid adenomas, their numbers increase.<sup>12</sup> Additionally, parathyroid has mast cells, lipid-bearing cells, and macrophages.

Parathormone is a polypeptide hormone weighing 8500 Da and consisting of 84 amino acids that are secreted from the chief cell. It regulates calcium metabolism by acting on three main target tissues such as bones, kidneys, and intestines. It inhibits phosphate (P) reabsorption by acting on renal tubules. Parathormone increases P and bicarbonate excretion and reduces Ca excretion. It activates 1 $\alpha$  hydroxylase enzyme, and increases Ca and P release from the bone. Additionally, it increases Ca and P absorption through vitamin D.

## Pathology

### *Hyperparathyroidism*

Hyperparathyroidism is the presence of increased levels of parathormone in the circulation as a result of an excessive amount of parathyroid hormone secretion. It can be primary, secondary, or tertiary. Additionally, hyperparathyroidism increases with age, and it is more common in women than in men.<sup>13</sup>

### *Primary hyperparathyroidism*

The most common cause of primary hyperparathyroidism is adenoma. Only one adenoma is seen in 80–85%, while more than one parathyroid adenoma occurs in 2–3% of patients. Parathyroid carcinoma is responsible for only 1% of cases.<sup>14,15</sup>

Primary hyperparathyroidism is initially asymptomatic, and a diagnosis must be made by analyzing the serum electrolytes, especially Ca. Over time, a wide range of nonspecific symptoms begin to appear, from nausea, vomiting, and fatigue to kidney stones, biliary stones, muscle weakness, and osteoporosis. Early diagnosis is important to prevent progression to chronic renal failure in irreversible conditions.<sup>15,17</sup> In the bones, initially, subperiosteal resorption and then cystic lesions are observed, and brown tumors are seen as a result of the bleeding inside them.<sup>16</sup>

Asymptomatic hyperparathyroidism and normocalcemic hyperparathyroidism are important issues that should be mentioned in primary hyperparathyroidism. In asymptomatic hyperparathyroidism, diagnosis is made using routine tests to identify an increase of Ca and PTH. PTH may be normal or 1–1.5 times normal.<sup>17,18</sup> Radiographically, there is no evidence other than a decrease in bone density.<sup>19</sup> Only 20% of patients have nonspecific symptoms such as renal calculi, fatigue,

proximal muscle weakness, and depression.<sup>20,21</sup> Ca is normal in normocalcemic hyperparathyroidism. However, PTH levels have increased. There is no other cause that can explain the hormone increase.<sup>22</sup> In such patients, diagnosis can be made using USG and computed tomography (CT) of the neck. These are the patients that need to be taken into consideration. There are many cases in the literature where the diagnosis is missed, and the condition of patients who were treated differently and had different diagnoses did not improve.

Another primary cause of hyperparathyroidism is parathyroid carcinomas that occur in less than 1% of cases. Clinical findings of carcinomas are more severe than adenomas or hyperplasia. In addition to the hyperparathyroidism symptoms mentioned above, parathyroid carcinomas can occur with subtle symptoms like peptic ulcers, tiredness, fatigue, and nausea with or without pancreatitis. Patients may die of hypercalcemia, and local invasion and metastasis are observed. A palpable mass is seen in 30–76% of cases with parathyroid carcinoma.<sup>23</sup> When the diagnosis is late, patients are often incurable or have treatment-resistant cases.<sup>24,25</sup>

### *Secondary hyperparathyroidism*

Secondary hyperparathyroidism is most commonly seen in patients with chronic renal failure. For renal failure, hyperplasia develops in the parathyroid gland after secondary hyperphosphatemia and hypocalcemia. As a result, secondary hyperparathyroidism causes calcification in the tissues.<sup>26,27</sup> Vitamin D deficiency is also another reason for tissue calcification. Phosphate binders, vitamin D, selective/non-selective vitamin D receptor (VDR) activators, and calcimimetic agents are used to treat secondary hyperparathyroidism. Surgical treatment is applied in cases where

there is no response to medical treatment, such as refractory Ca, PTH elevation, pathological fracture, itching, or bone pain.<sup>28</sup>

### **Tertiary hyperparathyroidism**

Tertiary hyperparathyroidism is the excess of PTH secretion that results from long-term exposure to hyperparathyroidism.

### **Parathyroid cysts**

Parathyroid cysts were first described by Sandstorm in 1880. Parathyroid cysts are divided into two groups: functional cysts, which secrete PTH, and non-functional cysts, which do not secrete PTH. Nonspecific complaints or symptoms related to hypercalcemia are seen, and its treatment is surgery.<sup>29</sup>

Gao et al. reported a case of acute pancreatitis in which a 22-year-old patient attended the hospital with urgent epigastric pain. The examination showed that the patient, who also had accompanying hypercalcemia, had a parathyroid carcinoma. Acute pancreatitis together with primary hyperparathyroidism is a very rare case. This case is reported in 1.5% of patients.<sup>30,31</sup>

Tagore et al.<sup>32</sup> also reported a case of acute pancreatitis and parathyroid carcinoma, which is also clinically rare, in an 88-year-old woman.

Bostan et al. presented the case of a 28-year-old woman who attended the hospital with fractures and whose diagnosis had been missed for 6 years. Nonspecific complaints such as malaise, fatigue, anorexia, and myalgia had not been detected in this patient who attended the hospital 6 years prior to this admission, and the patient, whose complaints had continued, began to lose weight. However, 6 years later, when biochemical parameters were studied, PTH and Ca were found to be high, and parathyroid adenoma was diagnosed following

imaging studies. The patient was then treated and her complaints resolved.<sup>33</sup>

Baek et al. reported concurrent parathyroid carcinoma and papillary thyroid carcinoma with schizophrenia. A 68-year-old female patient who had been diagnosed with schizophrenia 20 years before was diagnosed with parathyroid carcinoma and papillary thyroid carcinoma when elevated Ca and alkaline phosphatase levels were detected after imaging studies. After treatment, the patient's complaints and malaise decreased significantly.<sup>34</sup>

Pang et al. presented the case of a 68-year-old diabetic patient with depression, fatigue, peptic ulcer, and hypercalcemia. As a result of parathyroid imaging performed on the patient with normal parathormone, incidental parathyroid adenomas could be diagnosed. In cases where hypercalcemia is established, the importance of imaging studies has been emphasized.<sup>35</sup>

Chang et al. reported the case of a 49-year-old female patient who attended the hospital with chest pain. Biochemical test results showed high Ca and PTH levels, and scintigraphy showed parathyroid adenomas and papillary thyroid carcinomas that were located together.<sup>36</sup>

Gulcelik et al. reported the case of a 50-year-old female patient with diabetes. Despite the presence of mild hypercalcemia, her PTH level was normal. Parathyroid adenoma was detected by ultrasonography. This shows once more that clinical suspicion is important in detecting parathyroid masses.<sup>37</sup>

Nakano et al. reported the case of a 49-year-old patient with renal calculi who was diagnosed with hypercalcemia after biochemical examination. Parathyroid carcinoma was detected after imaging and histopathologic examination.<sup>38</sup>

## Conclusion

There are many cases in which the diagnosis is missed and the underlying parathyroid Ca cannot be detected, such as in the case reports that are discussed above, but treatment was attempted because of urolithiasis. Loss of time causes further symptom progression in the patients, local invasion of the underlying parathyroid mass, or patient loss because of hypercalcemia, or the patient's condition becomes inoperable.

Among these patients, parathyroid malignancies were detected using imaging tests that are conducted with simple biochemical tests. Clinicians should be mindful of parathyroid masses in patients with such nonspecific complaints and should consider simple electrolytes such as Ca and simple imaging methods such as USG.

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