CASE REPORT

Incidental finding of papillary thyroid carcinoma with BRAF^{V600E} mutation in a patient with coexistent primary hyperparathyroidism and Graves' hyperthyroidism

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SUMMARY

The simultaneous occurrence of hyperthyroidism and hyperparathyroidism was previously reported to be rare, but it was recognised more and more clearly by effective evaluations. Recent studies also mentioned the coexistence of parathyroid adenoma and papillary thyroid carcinoma (PTC). The potential mechanism is still unknown. We report a case of a 46-year-old man coexisted with primary hyperparathyroidism, Graves' hyperthyroidism and occult PTC. The patient had a 6-month history of polyphagia and irritability. Blood examinations showed elevated serum calcium and parathyroid hormone levels. Serum phosphate was lower. Thyroid function evaluation indicted Graves' hyperthyroidism. Ultrasound showed a solitary hyperchoic thyroid nodule in the right gland. Parathyroid radioisotope scanning found a mild enhancement of 99mTc absorption in the lower part of the right parathyroid gland. A surgical exploration was carried out and the parathyroid adenoma resection was performed. An occult micro-PTC with BRAF^{V600E} mutation was also detected.

BACKGROUND

The simultaneous occurrence of hyperthyroidism and hyperparathyroidism in a patient was previously considered to be rare. Only about 50 cases of such patient were well-documented in the literature until 1989.¹ Owing to the effective evaluation of preoperative ultrasound and postoperative pathology biopsy, detection of coexistence is easier than previously recognised.^{2–4}

In a retrospective study, the author reported that among patients who underwent hyperthyroidism surgery the concomitant rate of hyperparathyroidism was 13.5%.³ Recent studies also reported the rare coexistence of parathyroid adenoma and papillary thyroid carcinoma (PTC).^{5–7} In most of the reports, patients presented with or without symptomatic hyperparathyroidism preoperatively. Papillary thyroid carcinoma was usually diagnosed incidentally by intraoperative or postoperative pathology findings. In another retrospective study, Gul *et al*⁸ revealed that by postoperative pathological examination, particularly thyroid carcinoma was found concomitant in 15% of the patients with hyperparathyroidism. We report the case of a patient with a preoperative diagnosis of Graves' hyperthyroidism and hyperparathyroidism. Surprisingly, occult micro-PTC was found on

pathological examination. BRAF^{V600E} mutation, the hotspot mutation in PTC, was also detected by pyrosequencing analysis to investigate the potential association of this coexistence.

CASE PRESENTATION

A 46-year-old man was admitted to our hospital with a symptom of a 6-month history of polyphagia and irritability. The patient had progressive weakness, epigastric pain, nausea and acute body weight loss of 15 kg in the past month. He also had a 4-year history of hypertension. He did not have the history of neck irradiation or operation. Family history was unremarkable.

On admission, the patient was anxious. His mouth and tongue were dry. Neck examination revealed a mild enlargement of the thyroid gland which was non-tender on palpation and moved with deglutition. Upper abdominal tenderness was detected. Cardiological, pulmonary and neurological evaluations were normal.

Blood examinations showed elevated serum calcium (15.4 mg/dL; normal 8.4–10.0) and parathyroid hormone (PTH) levels (257.2 pg/mL, normal 15–65). Serum phosphate was lower (0.7 mmol/L, normal 2.8–4.7). Alkaline phosphatase level was elevated to 187 U/L (normal 36–110).

Kidney function was normal. Twenty-four hour urinary calcium and phosphate increased significantly to 2392 mg/day (normal 100–300) and 3178 mg/day (normal 499–1302), respectively. Thyroid function evaluation showed a decrease in the thyrotrophin level (<0.1 µU/mL; normal 0.25–5) with increased (free thyroxine 73.0 pmol/L; normal 9.1–25.5) and tri-iodothyronine level (26.5 pmol/L; normal 2.9–9.1); antithyroid antibodies were positive. On neck evaluation, ultrasound showed that the thyroid gland was mildly enlarged with chronic inflammation. A solitary hyperchoic thyroid nodule of 4 mm×5 mm was detected in the right gland with sharp border and regular morphology. The parathyroid gland appeared to be normal by ultrasound detection. Radioisotope scanning showed diffused enlargement of bilateral thyroid gland and mild enhancement of 99mTc absorption in the lower part of the right parathyroid gland, which indicated the possibility of hyperparathyroidism. The bone mineral densities of the lumbar spines and hip joint were 0.7 g/cm² (T-score -2.4, Z-score -2.2) and 0.9 g/cm² (T-score -0.6, Z-score -0.8), respectively.

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Figure 1 Light microphotograph showing micropapillary thyroid carcinoma in the thyroid gland (H&E stain; original magnification $\times 200$, scale bar=500 μm).

DIFFERENTIAL DIAGNOSIS

Calcium-sensing receptor resistance, multiple endocrine neoplasia type 2.

TREATMENT

Emergency treatment for hypercalcaemia crisis was started with hydration using physiological saline solution. Injection of salmon calcitonin and intravenous drip of pamidronate disodium were also used for decreasing the serum calcium level. Antithyroid drug methimazole, at an initial dose of 60 mg/day, was given to this patient. Lugol iodine was used for preoperative preparation. Serum calcium was reduced to normal range 3 days later. A surgical exploration was carried out. Total thyroidectomy and parathyroid adenoma resection were performed and the patient was stable after surgery. During the surgery, a solid nodule in the size of 12mm $\times$ 10 mm $\times$ 10 mm was detected behind the inferior pole of the right thyroid lobe, just outside the right recurrent laryngeal nerve. The nodule was confirmed to be parathyroid adenoma by pathology detection. The thyroid glands on both sides looked enlarged. A grey-coloured nodular was found in the right lobe. Surprisingly, the intraoperative frozen biopsy and postoperative H&E staining confirmed it to be micro-PTC (figure 1). L-thyroid at a dosage of 100 μg /day, oral calcium and vitamin D were also given to this patient after discharge.

OUTCOME AND FOLLOW-UP

The patient recovered well after the operation. Laboratory findings normalised rapidly after operation. His serum intact PTH

level decreased to 5.1 pg/mL. The calcium concentration reached 11.8 mg/dL 1 day after the surgery and decreased to 8.9 mg/dL at the third day postoperation. One year after the surgery, the patient has no discomfort. The serum thyroxine and calcium levels remained normal.

BRAF^{V600E} mutation detection

BRAF^{V600E} mutation is one of the most common genetic mutations in sporadic PTC, which have the high prevalence and specificity for PTC. To date, pyrosequencing-based assay for BRAF mutation detection have high accuracy and precision. The DNA of this patient was extracted from paraffin-embedded tissue on the right thyroid lobe as previously described by our laboratory.⁹ BRAF^{V600E} mutation was detected by pyrosequencing.¹⁰ The result was positive for BRAF^{V600E} mutation in the occult thyroid carcinoma (figure 2).

DISCUSSION

Concomitant thyroid diseases in patients with hyperparathyroidism have been reported and gained the recognition by more and more clinicians. Owing to the simultaneous involvement of both glands, clinical manifestations are complicated. Thus the disease frequently goes unrecognised. The patient in our case got serious hypercalcaemia crisis which reduced the contractility of smooth muscle and aggravate the symptoms of dehydration. The presenting symptoms of nausea, vomiting, weight loss and anxieties were originally interpreted as digestive disease. The possibility of primary hyperparathyroidism was not taken into consideration by the local physician until the detection of serum PTH. Symptoms of hyperthyroidism, including obvious weight loss and irritability, were also neglected until thyroid nodular examination by ultrasound.

Preoperative evaluation is important for the choice of therapeutic strategy. Ultrasound was reported to have a high positive predictive sensitivity of 83.5% in the diagnosis of parathyroid adenoma.¹¹ However, experience of the examiner, location and size of the adenoma may affect the sensitivity of detection in our patient. Tc99 scanning helped us confirm the final diagnosis of the parathyroid adenoma. Moreover, it is also necessary to pay attention to the solitary thyroid nodule found by ultrasound. Fine-needle aspiration biopsy is recommended for the evaluation of solitary thyroid nodules for its cost-effective benefit.¹² Operation was recommended to cure thyroid and parathyroid diseases. In addition, the nodular size was less than 10 mm, fine-needle aspiration was not performed for this patient. PTC was an unexpected finding in the surgery.

Until now, it is still unclear why hyperthyroidism occurred with hyperparathyroidism. In most cases, thyroid nodular or hyperplasia was detected by interoperative or postoperative detections.^{5–7} Some authors believed the occurrence of this

Figure 2 Pyrosequencing analysis showed representative BRAF^{V600E} mutation (arrow indicates the mutated nucleotide).

association was just a coincidence.¹³ Others advocated that the endogenous calcium level, growth factors and genetic factors may involve.¹⁴ In addition, the initial connection between the parathyroid adenoma and PTC is unknown. Some authors assumed the oncogenic effect of hypercalcaemia on the thyroid gland may be associated.¹⁵ In a recent retrospective study, Lee *et al*⁵ summarised the concurrence of parathyroid adenoma and PTC on seven patients. Among them, no patient had the history of head or neck irradiation or surgeries. The author did not consider the oncogenic effect of hypercalcaemia applicable in their patients.

Previous literature also reported the rare association of toxic multinodular goitre with PTC and primary hyperparathyroidism.¹⁶ The author did not examine the aetiological relationship on a genetic basis but triggered the search for any other two pathologies while finding the presence of one disease. To our limited knowledge, our case is the first report of coexistence of primary hyperparathyroidism, Graves' hyperthyroidism and papillary carcinoma in one subject. For this patient, the mutation of BRAF^{V600E} indicated the genetic predisposition of PTC. This result suggests that functional parathyroid adenoma and papillary carcinoma may be aetiologically independent. However, the association of this incidence of PTC and hypercalcaemia is still uncertain. Further researches with larger sample size are needed.

Learning points

- Early consideration of the concomitance of hyperparathyroidism in patients with thyroid disease is helpful for the diagnosis.
- Thorough preoperative evaluation of the thyroid gland in a patient with primary hyperparathyroidism is important.
- Surgical investigation is recommended for curing both diseases in coexisting hyperthyroidism and hyperparathyroidism.

Competing interests None.

Patient consent Obtained.

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