Spontaneous Remission After a Hypercalcemic Crisis Caused by an Intracystic Hemorrhage of Bilateral Parathyroid Adenomas: A Case Report and Literature Review

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Background: Hyperparathyroidism is a common cause of hypercalcemia; however, spontaneous remission after a hypercalcemic crisis caused by an intracystic hemorrhage of parathyroid adenomas is very rare. The question, then, is “What is the best treatment strategy for this type of case?”

Method: A 47-year-old male patient with primary hyperparathyroidism and a hypercalcemic crisis caused by a hypercalcemic crisis was reported. Hypercalcemia was spontaneously relieved thereafter. Postoperative paraffin pathology results indicated an intracystic hemorrhage of bilateral parathyroid adenomas.

Results: After the case report, a literature review is also included to summarize the clinical features of this patient and to provide special reference for clinical diagnosis and treatment of similar cases.

Conclusions: The choice of surgical timing for such cases can be made based on the comprehensive consideration of clinical symptoms and changes in parathyroid function.

Keywords: hypercalcemic crisis, spontaneous remission, hemorrhage, parathyroid adenoma, primary hyperparathyroidism
INTRODUCTION

Hyperparathyroidism is the most common cause of hypercalcemia, but spontaneous remission after a hypercalcemic crisis caused by hemorrhage of parathyroid adenomas is very rare. There have been no reports involving an intracystic hemorrhage of bilateral parathyroid adenomas. It is generally believed that hemorrhage of parathyroid adenomas may be caused by rapid tumor growth with an insufficient blood supply to the tumor (1). The patients may present with a diversity of clinical features due to differing degrees of hemorrhage and necrosis of the parathyroid adenoma cells (2). Indeed, there has not been a literature review on the appropriate clinical decision for spontaneous remission of parathyroid function following an intracystic hemorrhage of parathyroid adenomas.

CASE DESCRIPTION

A 47-year-old male patient was referred to onset of excessive thirst and polydipsia more than 1 month ago, accompanied by general malaise and anorexia. Two weeks ago he went to a local hospital due to abdominal discomfort and the blood biochemical test revealed both elevated serum creatinine (172.9 umol/L, Ref. 63-109 umol/L) and calcium level (4.66 mmol/L, Ref. 2.1-2.7 mmol/L), a declined phosphorus level (1.76 mmol/L, Ref. 0.81-1.45 mmol/L). The blood sodium, potassium, and glucose levels were all normal. The patient was then referred to our hospital for further evaluation. The patient was previously healthy, without psycho-social disease, trauma history, nor drug use. He also denied the family history of hypercalcemia. Physical examination revealed the following: T, 36.5°C; P, 91/min; R, 20/min; and BP, 139/96 mmHg. No abnormalities were detected on examination of the heart, lungs, and abdomen. There was a grade II goiter (Figure 1A), with a 4 x 4 cm mass palpable in front of the neck. The masses had hard texture with poor mobility and no tenderness. The results of blood biochemical testing on the day after admission were as follows: creatinine 195 umol/L; estimated glomerular filtration rate 34.3 ml/min/1.73m²; calcium 3.80 mmol/L; phosphorus 1.24 mmol/L; and PTH, 320.7 pmol/L (Ref. 1.6-6.9 pmol/L).

The patient was given isotonic saline infusion (200 to 300 mL/hour) to correct volume depletion, a loop diuretic (furosemide (20 mg iv qd for 2 days)) to increase calcium excretion, and a single dose of salmon calcitonin (300 IU ivgtt). Third day after admission, the patient’s serum calcium level decreased to 2.17 mmol/L and the PTH level was 182.5 pmol/L. Then rehydration and calcium-lowering therapy were stopped, and the serum calcium concentration was monitored every one to two days. During the next one week the serum calcium levels had been within the normal range and phosphorus level fluctuated between 0.36 and 0.50 mmol/L. The serum creatinine levels returned to normal and PTH gradually decreased, but still above normal (Figure 2).

A CT scan of the neck (Figure 1B) revealed bilateral slightly hypointense cystic mass deep the thyroid, 4.4 x 3.2 cm size on the right, 4.2 x 2.1 cm size on the left, with a uniform density and clear borders. A contrast-enhanced scan revealed intracystic septa within the lesions, with apparent enhancement of the cystic wall and septa. An ultrasound examination of the neck revealed mixed cystic-solid nodules posterior to the two lateral lobes of the thyroid, the size was 5.0 x 2.3 x 3.7 cm(right) and 5.3x3.5x3.1cm(left) respectively. Both nodules had clear borders and a regular morphology without apparent internal blood flow signals. Contrast-enhanced ultrasound of neck mass shows mixed cystic-solid nodules behind the two lateral lobes of the thyroid. SPECT/CT fusion imaging (Figures 1C, D) revealed an abnormal increase uptake during MIBI in part of the mass posterior to the right lobe of the thyroid, which point the possibility of parathyroid adenoma. A bone density test and X-ray examination of the hands and four limbs did not demonstrate a reduction in bone mass and osteoporosis. At 11th day post-admission, the patient underwent an ultrasound-guided biopsy of the bilateral cystic nodules posterior to the thyroid. Ten milliliters of dark red bloody fluid were collected from the cystic nodules bilaterally. Exfoliative cytology indicated a small number of hyperplastic epithelial and tissue cells, possibly indicating benign cystic lesions. The neck masses shrank in size after fine needle aspiration; however, ultrasonography of the thyroid gland 2 days later revealed cystic space regains its size before aspiration which suggested new hemorrhage after the fine needle aspiration.

According to the guidelines for the diagnosis and treatment of primary hyperparathyroidism (3) and considering the patient’s surgical requirements, the neck mass resection was performed at three weeks post-admission, during which the bilateral cystic-solid masses were found, 5 x 3 x 3.5 cm in size on the right (Figure 1E) and 5.5 x 4 x 3.5 cm on the left (Figure 1F). The mass adhered closely to the thyroid gland and the surrounding tissues, with obscure borders and an irregular morphology. At last, the patient underwent resection of bilateral inferior parathyroid adenomas and a total thyroidectomy. Bilateral superior parathyroids were preserved. Postoperative paraffin pathology results indicated intracystic hemorrhage of bilateral parathyroid adenomas. (Figures 1G, H). Thyroid pathology suggested nodular goiter in both bilateral lobes and isthmus of the thyroid gland.

The patient recovered well after surgery. At day 1 post-operatively, the serum PTH level was 1.95 pmol/L, and the blood calcium level was 2.23 mmol/L. According the clinical guideline, The patient was given calcitriol [1,25(OH)2D] 0.5ug twice daily, calcium supplement (10% calcium gluconate 100ml diluted intravenous infusion each day) after surgery. At 2 and 4 days post-operatively, the blood calcium level was 1.87 and 1.65 mmol/L, respectively, and the patient had no tetany. At 9 days post-operatively, the normal blood calcium level was restored and discharged from hospital with oral calcium carbonate 600mg twice daily and osteopontin 0.5ug twice daily. The blood calcium and PTH levels were monitored at 3 weeks, 2 months, 4 months, post-operatively and the results were all normal. The dose of the above drugs was reduced at month 4 and then discontinued at month 5. Calcium and phosphorus were still normal at the 6th month recheck.
There was a grade II goiter (A), with a 4 x 4 cm mass palpable near the thyroid bilaterally. CT scan (A, B) of the neck revealed bilateral slightly hypointense cystic shadows below the thyroid. SPECT/CT fusion imaging (C, D) revealed an abnormal increase in uptake in part of the mass behind the right lobe of the thyroid during MIBI, which was considered relevant to hyperparathyroidism. There were a cystic-solid mass (E) on the posterolateral aspect of the right lateral lobe of the thyroid and a cystic-solid mass (F) on the left lateral lobe of the thyroid. Postoperative paraffin pathology (HE staining x100) results indicated that both the right (G) and left (H) space-occupying lesions represented parathyroid adenomas with cystic change.
Through screening tests, the patient was finally ruled out multiple endocrine neoplasia. He and his relatives also underwent testing of genes associated with MEN, none were carriers of the MEN related genes.

DISCUSSION

The Mismatch Between Tumor Rapid Growth and Blood Supply Might Result in Infarction of Parathyroid Adenoma and Hemorrhage

Intracystic hemorrhage of parathyroid adenomas is very rare. There are only about 100 cases reported with intracystic hemorrhage of parathyroid adenomas in the literatures. Some studies have shown that the use of anti-coagulation drugs (4), non-steroidal anti-inflammatory drugs (5) and trauma (6) may be risk factors; however, the cause of intracystic hemorrhage of parathyroid adenomas is unknown. It is currently believed that if tumor growth is too rapid and the blood supply to the tumor is insufficient, hemorrhage of parathyroid adenomas may occur (1). In 1953, Howard reported spontaneous remission after hyperparathyroidism due to infarction in parathyroid adenomas (7), which was called Parathyroidectomy. Nylen (8) suggested that infarction and hemorrhage represented two stages of the same phenomenon. Parathyroid adenoma apoplexy is divided into infarction of the adenoma (without hemorrhage), infarction with intracystic hemorrhage, and extracystic hemorrhage (8).

For our patient, he was in good health before and without trauma nor drug use history. Combined with the changes of blood calcium level, it is speculated that the rapid growth of adenoma and the massive release of PTH lead to the hypercalcemic crisis. However, the mismatch between tumor growth and blood supply resulted in infarction of parathyroid adenoma and intracystic hemorrhage, followed by spontaneous remission of hyperparathyroidism and hypercalcemia crisis.

The Clinical Manifestations of Bleeding Parathyroid Adenomas and the Accompanying Changes in Parathyroid Function Are Diverse

Symptoms of hemorrhage of parathyroid adenomas depend on the speed and volume of hemorrhage, as well as the position of the parathyroid gland (in situ or ectopic). Simple necrosis of parathyroid adenomas is associated with a smaller hematoma and few local symptoms. This condition may remain undetected until an incidental finding of spontaneous remission of hypercalcemia (9). Some patients are free from local discomfort in intracystic hemorrhage of in situ parathyroid adenomas (2), and may present with neck pain, a mass, and hoarseness (2). In in situ extracystic hemorrhage, the blood may diffuse to the neck or mediastinum, leading to compression of tracheal and esophagus (2), may cause dyspnea and dysphagia. Compression of the recurrent laryngeal nerve will lead to hoarseness and vocal cord paralysis with local swelling, pain, a mass, and ecchymosis (2). Spread of the hematoma may cause a pleural effusion (10, 11). Life-threatening hemorrhage of parathyroid adenomas usually needs surgical treatment as soon as possible. Hemorrhage of ectopic parathyroid adenomas often leads to a mediastinal hematoma, (6, 11–16) which also requires emergency surgery.

Parathyroid adenoma cells may also be involved and become necrotic after necrosis and hemorrhage of parathyroid adenomas, so parathyroid function will be influenced too. The
changes of parathyroid function vary to what extent the adenoma cells are involved. Some patients with hypercalcemia fail to achieve remission (17–19) or even progress to refractory hypercalcemic crisis (20). Others with hypercalcemia may show a reduction in the PTH level and achieve remission or even have the blood calcium level restored to normal (7, 21). In a few cases, hungry bone syndrome may occur due to the rapid decrease in the PTH level, leading to hypocalcemia (2, 22–24). Patients with hyperparathyroidism and complete necrosis of the parathyroid adenoma usually achieve full remission (21, 24–28), i.e., parathyroid adenectomy in the real sense; however, some patients with hypercalcemia only achieve temporary remission and relapse later (22, 24, 27, 29). The time of relapse varies from one patient to another and ranges from several weeks to several years. The longest reported time of relapse after remission is 7 years (30).

In our case, only bilateral thyroid mass was present because of bilateral in situ parathyroid adenoma intracystic hemorrhage. Bone X-ray and bone density testing did not reveal bone mass changes in our case, indicating a relatively short course of disease of hyperparathyroidism. This patient showed a significant increase in the PTH level upon the onset, indicating rapid growth of the parathyroid adenoma and the secretion of a large amount of hormone before the hemorrhage. The blood calcium level was restored spontaneously to normal after the hemorrhage and recurrent hematoma exists. The blood calcium level was restored to normal (7, 21). In a few cases, there was no further decrease in the PTH level beyond 50-60 pmol/L. Based on an increased growth of the parathyroid adenoma and the secretion of a large amount of hormone before the hemorrhage. The blood calcium level was restored spontaneously to normal after the hemorrhage and recurrent hematoma exists. In addition, there are two case reports on hemorrhage of parathyroid adenomas after fine needle aspiration biopsy so far. One of them was followed up for 105 months, and finally achieved full remission of hyperparathyroidism after hemorrhage of the parathyroid adenoma (25), the other case received surgical treatment at 1 month after aspiration-reduced hemorrhage (36).

Therefore, we believe that fine-needle aspiration biopsy of parathyroid adenoma hematoma is of limited diagnostic value and carries some risk. For patients requiring fine needle aspiration for decompression, the decision should be made carefully by weighing the pros and cons, unless the compression symptoms are severe and urgent.

Through Literature Review, It Is Believed That There Is No Consensus On the Timing of Surgery for Intracapsular Hemorrhage in Primary In Situ Parathyroid Adenomas and That a Comprehensive Assessment Should be Made Based on the Clinical Features of the Case and the Patient’s Wishes

In our case, it was found that the parathyroid adenoma adhered closely to the surrounding tissues and the hematoma tension was high. Both of the hematomas burst open during the surgery. Considering the hyperparathyroidism may relieve after intracystic hemorrhage of parathyroid adenoma and the difficulty of surgery in the acute phase, as well as the risk of extracapsular hemorrhage due to hematoma rupture, we conducted a literature review to answer the following questions. Do these patients require aggressive surgery? What is the appropriate time for surgery?

There has been no consensus on the choice of surgical timing for intracystic hemorrhage of primary in situ parathyroid adenomas.
According to previous literature reports, some cases had severe adhesions following intracystic hemorrhage of the parathyroid adenomas, as noted during surgery (6, 8, 37). One such case underwent surgery 7 months after the onset (38). The evidence is still insufficient to prove that prolonging conservative treatment can reduce adhesions found by subsequent surgery. In another report (37), a parathyroid adenoma (6.9 cm x 5.2 cm x 4.8 cm) ruptured during surgery. A large amount of unclear and bloody fluid flowed out, as was observed in our case; however, there have been no case reports on extracystic hemorrhage of a parathyroid adenoma due to hematoma rupture during the conservative treatment for intracystic hemorrhage of parathyroid adenomas.

Whether the patients underwent surgery after intracystic hemorrhage of parathyroid adenomas, and the specific duration of conservative treatment vary across the literature reports. We reviewed literature reports on 120 cases with hemorrhage or necrosis of parathyroid adenomas (including primary and secondary hyperparathyroidism, in situ ectopic parathyroid adenomas, and intracystic and extracystic hemorrhage of the parathyroid adenomas). Among the cases, we performed a detailed analysis of 34 cases with clinical or pathologic diagnosis of intracystic hemorrhage or necrosis of in situ primary parathyroid adenomas, parathyroid cysts and hyperplasia, described in Chinese or English (Tables 1, 2). Of these cases, 12 did not undergo surgical treatment and all of them achieved spontaneous remission of hyperparathyroidism (Table 1). Five patients achieved full restoration of parathyroid function and complete absorption of the lesions. Four patients were followed up for 6, 9, 16, and 29 months, and none relapsed. Three patients relapsed at 16 days, 1 year, and 2 years afterwards, although the patients had not undergone surgical treatment upon the time of the literature report. Eight patients finally underwent surgical treatment after conservative treatment. Among the 8 patients, 4 achieved spontaneous remission of hyperparathyroidism, but later underwent surgical treatment due to recurrent hyperparathyroidism at 1 month, 6 years, 20 months, 11 months, and 8 years later. One patient underwent surgery at 2 months after conservative treatment due to failure to achieve remission of hyperparathyroidism; 2 patients achieved remission of hyperparathyroidism to a certain degree, but still received surgical treatment after 1 month and 3 months of conservative treatment, respectively. There were some patients who directly received surgical treatment, but the duration of conservative treatment before surgery was not mentioned in the literature. All patients had their parathyroid adenomas resected en bloc and achieved full remission of hyperparathyroidism after surgery. Whether hyperparathyroidism can be relieved, and hyperparathyroidism will recur later are independent of the size of the hematoma.

### TABLE 1 | Case analysis of intracystic hemorrhage or necrosis of in situ primary parathyroid adenomas (Unoperated patients, n = 12).

| Author          | Age | Sex | Signs/symptoms                          | Hematoma size (cm) | [Ca++] | PTH    | Surgery | Follow-up time | Changes in PHPT | Clinic Diagnosis                           |
|-----------------|-----|-----|----------------------------------------|--------------------|--------|--------|---------|---------------|-----------------|------------------------------------------|
| Wootten (2)     | 63  | M   | tetanic contractures of the hands      | N/A                | 9.4 mg/dL | 168 pg/mL | N      | 6M            | Spontaneous remission                     | spontaneously resolving primary hyperparathyroidism, parathyroid apoplexy. |
| Nylen (9)       | 64  | M   | Abrupt neck swelling and pain, neck tenderness | 1.58               | 8.6 mg/dL | 27 pg/mL | N      | 16M          | Spontaneous remission                     |                                        |
| Baskar (9)      | 30  | F   | Chronic symptomatic hypercalcemia      | N/A                | 2.37 mmol/L | 2255 pmol/L | N      | 5Y            | Spontaneous remission                     | MEN1                                     |
| Ferrari (21)    | 48  | M   | symptoms of severe symptomatic hypercalcemia | 2.8                | 118 mg/dL | 11315 pg/mL | N     | 2Y            | Spontaneous remission                     | parathyroid apoplexy                    |
| Micale Sara J   | 71  | F   | neck discomfort, sore throat, difficulty swallowing symptoms of severe symptomatic hypercalcemia | 2.1 × 2.4 × 3.6 | 8.1 mg/dL | —64.3 pg/mL | N     | 16D          | Spontaneous remission                     | infarction of parathyroid adenoma       |
| Novovorsky (24) | 54  | F   | symptomatic hypocalcaemia               | 4.4                | 1.88 mmol/L | 117.6 pmol/L | N      | 11M          | Spontaneous remission                     | Infarct hemorrhage of parathyroid adenoma, hemorrhage of parathyroid adenoma | |
| Kara (23)       | 67  | F   | slight neck swelling                    | N/A                | —9.3 mg/dL | 190.1 | N      | 105M         | Spontaneous remission                     | Infarct hemorrhage of parathyroid adenoma, hemorrhage of parathyroid adenoma |     |
| Schinner (23)   | 68  | M   | Chronic symptomatic hypercalcemia       | 3.7 × 1.2 × 1.7 | 3.3 mmol/L | 19.7 pmol/L | N     | 4Y            | Spontaneous remission                     | Infarct hemorrhage of parathyroid adenoma, parathyroid adenoma infarction |     |
| Onoda (23)      | 67  | F   | Asymptomatic                            | 1.4X1.1X1.0       | —         | —     | N      | 2Y            | Spontaneous remission                     | Infarction of parathyroid adenoma       |
| Lucas (29)      | 53  | F   | Acute neck pain, dysphagia, neck mass dyspnea | 3                  | —8.6 mg/dL | —38 pg/mL | N     | 10M          | Spontaneous remission, but recurrence in 10 months | infarction of parathyroid adenoma       |
| Kovacs (39)     | 49  | F   | Abrupt neck pain, dyspnea,tenderness    | N/A                | 2.17 mmol/L | 16.41 (1.38-5.72) pmol/L | N | 29M          | Spontaneous remission                     | infarction of the parathyroid adenoma | Parathyroid apoplexy                   |
| Chan (40)       | 78  | F   | Chronic symptomatic hypercalcemia       | 2.5 × 1.5         | 1.37 mmol/L | 132.5 pmol/L | N     | 1Y            | Spontaneous remission, but recurrence in 1 year |                                       |

* Total calcium; †Corrected calcium; PTH, parathyroid hormone; ↓Below normal; ↑Above normal; —Within the normal range.
| Author       | Age | Sex | Signs/symptoms                                      | Hematoma size (cm) | [Ca++] | PTH | Surgery                  | Time before operation | Changes in PHPT               | Pathological diagnosis                                      |
|--------------|-----|-----|----------------------------------------------------|--------------------|--------|-----|--------------------------|----------------------|---------------------------|-------------------------------------------------------------|
| Howard (7)   | 57  | F   | neck pain, nausea, vomiting and tachycardia        | 3.5x2x2            | ↑20 mg, per 100 ml | N/A | surgery                  | N/A                  | Spontaneous remission after Hypercalcemia                  | infarction of the adenoma                                  |
| DeGroote (17)| 45  | F   | symptomatic hypercalcemia, suddenly neck pain, neck| 3x3                | 20 mg/100 ml      | N/A | Neck exploration          | 4D                   | N/A                       | parathyroid adenoma, chief cell type, with a fresh hemorrhag |
| Chodack (18) | 61  | F   | symptomatic hypercalcemia, gradual increase in      | 6.5x4              | ↑18.5 mg/100 cc   | N/A | emergency exploration    | emergency exploration| N/A                       | 1.5-cm cystic area and multiple areas of cystic necrosis    |
| Mizunashi (20)| 62 | F   | progressive symptomatic hypercalcemia, confusion    | 2.5x2.0x1.8        | ↑14.25 mmol/L     | ↑2300 ng/L | surgery                  | Emergency operation | Intractable hypercalcemia                                  | within the gland chief-cell parathyroid adenoma           |
| Johnston (22)| 19  | M   | tetany, neck                                      | 3.5x2.5            | ↓5.1 mg, per 100 ml| N/A | surgical exploration     | N/A                  | N/A                       |                                                                             |
| Novodvorsky (24)| 51| M   | Asymptomatic                                      | 1.7 ×0.5 ×1.0      | ↓2.43 mmol/L      | ↑8.7 pmol/L | uneventful bilateral neck exploration | 20M                  | spontaneous remission, but recurrence in 17 months          | parathyroid adenoma with intratumoral hemorrhage           |
| Cetani (27)  | 39  | F   | neck pain, swelling, tenderness                    | 2.5                | ↓1.23mmol/L       | ↓40 ng/L   | parathyroidectomy        | 11M                  | parathyroid adenoma                                        |                                                                             |
| Lucas (29)   | 67  | M   | Chronic symptomatic hypercalcemia                  | 1.5x1.0            | ↓9.9mg/dL         | ↑167 pg/ml | Neck exploration          | N/A                  | Spontaneous remission                                       | Spontaneous infarction of a parathyroid adenoma           |
| Pereira (30) | 24  | F   | hand muscle contraction, Chvostek’s sign           | 7.4 cm3            | ↓6.8 mg/dl        | ↑110 pg/ml | bilateral neck exploration | 8Y                   | spontaneous remission, but recurrence in 7 years             | benign proliferation of parathyroid cells                  |
| Daniel (31)  | 51  | F   | intermittent hoarseness, breathy voice, coughing,  | 3.4                | 10.8 mg/dL        | 118 pg/mL | minimally invasive        | N/A                  | hypercellular parathyroid tissue                           |                                                                             |
| Taguchi (33) | 85  | F   | neck mass and symptomatic hypercalcemia            | 3.6                | ↑11.7 mg/dl       | ↑1348 pg/ml | surgery                  | N/A                  | cystic parathyroid adenoma with intracystic hemorrhage      |                                                                             |

(Continued)
As shown by the literature review, conservative observation may be feasible for those achieving spontaneous remission of hyperparathyroidism after intracystic hemorrhage of a parathyroid adenoma. Given the probability of relapse, the parathyroid function and hematoma changes should be closely monitored. Surgical treatment is recommended if hyperparathyroidism recurs. Those failing to achieve remission of hyperparathyroidism after the hemorrhage can be treated by elective surgery. The choice of surgical timing should be made based on parathyroid function, health economics considerations, and the patient’s will.

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CONCLUSION

We present a case of a 47-year-old male patient with primary hyperparathyroidism and a hypercalcemic crisis, and hypercalcemia spontaneously relieved thereafter. Pathology results indicated an intracystic hemorrhage of bilateral parathyroid adenomas. The mismatch between tumor rapid growth and blood supply might result in infarction of parathyroid adenoma and hemorrhage. The clinical manifestations of bleeding parathyroid adenomas and the accompanying changes in parathyroid function are diverse, because of the diversity of speed and volume of hemorrhage, as well as the position of the parathyroid gland. Fine-needle aspiration biopsy of parathyroid adenoma hematoma is of limited diagnostic value and carries some risk. After literature review, it is believed that there is no consensus on the timing of surgery for intracapsular hemorrhage in primary in situ parathyroid adenomas and that a comprehensive assessment should be made based on the Clinical manifestations, changes in parathyroid function and the patient’s wishes. We will continue to collect such case reports and keep the literature review updated to provide the best evidence for clinical decision making.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article-supplementary material. Further inquiries can be directed to the corresponding authors.

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ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of West China Hospital, Sichuan University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YL was involved in study concept, study design, and manuscript preparation. JL carried out the definition of intellectual content and manuscript review. HL handled data analysis and statistical analysis. HY carried out data acquisition. JQ and TWe conducted the clinical studies. TWa was involved in the literature research and manuscript editing. YY performed the role of guarantor for the integrity of the entire study. All authors contributed to the article and approved the submitted version.

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