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Parathyroidectomy failures and causes evaluation

Mohamed Baayou [1,2], Mohamed Bashagha[3], Mostafa Sgheir[4,5], Eltaher Elshagmani[6,7]

1- Department of Medicine, Faculty of Medicine, Misurata university, Libya
2- Department of Medicine, Misurata Medical Center Misrata, Libya
3- Department of radiology, Faculty of Medicine, Misurata university, Libya
4- Department of Surgery, Misurata Medical Center Misrata, Libya
5- Department of Surgery, Faculty of Medicine, Misurata university, Libya
6- Department of medical laboratory, Faculty of Medical Technology, Misurata, Libya
7- Department of medical laboratory, National cancer instittue, Misurata, Libya

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Abstract

Background: Persistent primary hyperparathyroidism (PHPT) after surgery is often due to missed ectopic or supernumerary glands. Reoperation is challenging and requires precise imaging, anatomical understanding, and surgical expertise.

Methods: A 34-year-old woman with classic PHPT symptoms and biochemical evidence (Ca: 12.75 mg/dL, PTH: 891 pg/mL) underwent two failed parathyroidectomies. Imaging was inconclusive; histology showed nodular hyperplasia in the first and absence of parathyroid tissue in the second. A third surgery, guided by high-resolution ultrasound and intraoperative endoscopy, located an ectopic retroesophageal adenoma, which was excised.

Results: Immediate postoperative laboratory confirmed cure (Ca: 7.2 mg/dL, PTH: <1.2). The patient developed transient hungry bone syndrome. No complications were noted.

Conclusion: Persistent PHPT requires high suspicion for ectopic or supernumerary glands. Third-time parathyroidectomy, when planned with expert imaging and surgical collaboration, can be safe and curative.

I) Introduction

The parathyroid glands were first identified by Sir Richard Owen in the Great Indian Rhinoceros in 1850 [1]. They were identified in humans by Ivar Sandstrom, a Swedish medical student, in 1880 [2]. The first parathyroidectomy was reported by Mandl in 1929, 30 years prior to the isolation of human parathyroid hormone [3].

The success of the surgical management of parathyroid disease is based on accurate biochemical diagnosis and the surgeon's expert understanding of the significant embryologic variations in parathyroid anatomy. Knowledge of the unusual anatomic locations for enlarged parathyroid glands is crucial to operative success during both initial and reoperative parathyroid surgery [3].

Bone disease in severe primary hyperparathyroidism (PHPT) is described classically as osteitis fibrosa cystica (OFC). Bone pain, skeletal deformities and pathological fractures are features of OFC. Bone mineral density is usually extremely low in OFC, but it is reversible after surgical cure. The signs and symptoms of severe bone disease include bone pain, pathologic fractures, proximal

muscle weakness with hyperreflexia. Bone involvement is typically characterized as salt-and-pepper appearance in the skull, bone erosions and bone resorption of the phalanges, brown tumors and cysts. Severe symptomatic PHPT, marked by elevation of the serum calcium and PTH concentrations and sometimes nephrolithiasis and nephrocalcinosis [4].

Normal glands are usually approximately 5 x 4 x 2 millimetres in size and weigh 35-50 mg. Enlarged gland can be 50 mg to 20 grams in weight. The superior parathyroid glands are derived from the fourth branchial pouch. The inferior parathyroid glands are derived from the third branchial pouch [4]. Most (84 %) individuals have four parathyroid glands, two superior and two inferior glands [5]. Additional glands are found in 13 % of patients and ≤3 % only three glands [5]. The superior glands are symmetric in 80 % of cases, and inferior glands are symmetric 70 % of cases [5].

During parathyroid exploration, deductive reasoning based on the embryologic origin of identified parathyroid glands helps the surgeon identify missing glands [4]. The ectopic gland may be one of the four parathyroid glands, or it may be a supernumerary gland. In one series of 102 patients with persistent or recurrent hyperparathyroidism who required reoperation, ectopic glands were found in the paraesophageal position (28 %), in the mediastinum (26 %), intrathymic (24 %), intrathyroidal (11 %), in the carotid sheath (9 %), and in a high cervical position (2%) [7].

An ectopic superior parathyroid gland may be undescended and located at the piriform sinus or intrathyroidal. Ectopic inferior parathyroid glands can be undescended at the carotid bulb. More typically they will be found lateral and inferior to the middle to lower thyroid lobe adjacent to the thyrothymic tract. Ectopic inferior parathyroid glands are most often found in the thymus or mediastinum (9 %) [8]. An undescended inferior parathyroid gland may be located anywhere within the carotid sheath (2 %). They can also be located intrathyroidally (1 %).

Supernumerary (>4) parathyroid glands occur in 2.5 to 15 % of individuals [5,9]. They can range from five to eight in number [6]. Most supernumerary glands are small, rudimentary, or divided, when enlarged, may be responsible for persistent hyperparathyroidism after failed parathyroid exploration [5,10,11]. Supernumerary glands were found in 15 % of cases of persistent hyperparathyroidism after parathyroidectomy [9]. The most common location of supernumerary glands is within the thymus or in relation to the thyrothymic ligament (two-thirds of cases) [6,11].

Missed parathyroid adenoma is the most common cause for a failed initial parathyroid operation and persistent hyperparathyroidism [12]. Understanding the embryology and anatomy of the parathyroid glands will help determine which one of the four parathyroid glands is missing or if it is a supernumerary gland. In this study, a case report will be demonstrated and the causes parathyroidectomy failure will be discussed.

II) Case history

A 34-year Libyan lady from southeast of Libya not known to have any chronic illness presented to my clinic on 10/04/2021. Anamnesis revealed generalized bone pain, history of non-union fracture of right femur and humorous, limping gait and worsening symptoms of depression. The patient was alert but slow and complained of nausea. Serial of laboratory investigations was requested (seeTab-1).

Tab-1 pre-operative laboratory investigations

Blood tests	Results
WBC	5.8 x10^9 /L
HB	13.2 g/dl
Platlets	283.000 10^9 /L
Serum creatinie	0.6 mg/dl
Blood urea	23 mg/dl
Serum corrected calcium	12.75 mg/dl
Serum phosphorus	2.4 mg/dl
Serum magnesium	2.58 mg/dl
24-hour urinary calcium	31 mg/dl
Intact PTH	891 pg/ml
25-OHD	67.4 ng/mL
TSH	1.8 µU/mL
Arterial blood gases	Normal no acidosis
Prolactin	14.8 ng/ml

A diagnosis of PHPT was made (high calcium and high PTH). Chest and abdominal X-ray was normal. Electrocardiogram normal and QTc: 408 ms. Neck USG showed sub centimetric iso-echoic thyroid nodules with peripheral vascularization, and no enlarged parathyroid glands. Abdominal ultrasound did not show kidney stones. X-ray hands (see Figure 1-A-B), distal clavicles (figure 2-A-B) and skull (Fig-3).

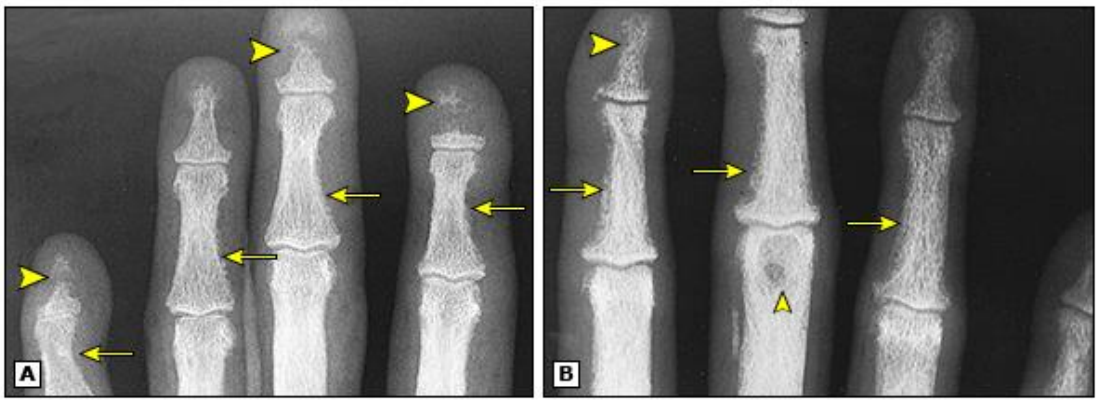

Fig-1 (A and B), osteroanterior (PA) hands. Note the radial margins of the proximal and middle phalanges bilaterally are frayed, irregular, and lace-like (arrows) owing to characteristic subperiosteal resorption. Also note the brown tumor (small arrowhead) and osteolysis of the distal phalanges (large arrowheads).

Fig. -2 (A) Detail view of the hands shows subperiosteal resorption in the phalanges (arrows). (B) Detail views of both distal clavicles show subchondral resorption bilaterally (arrows).

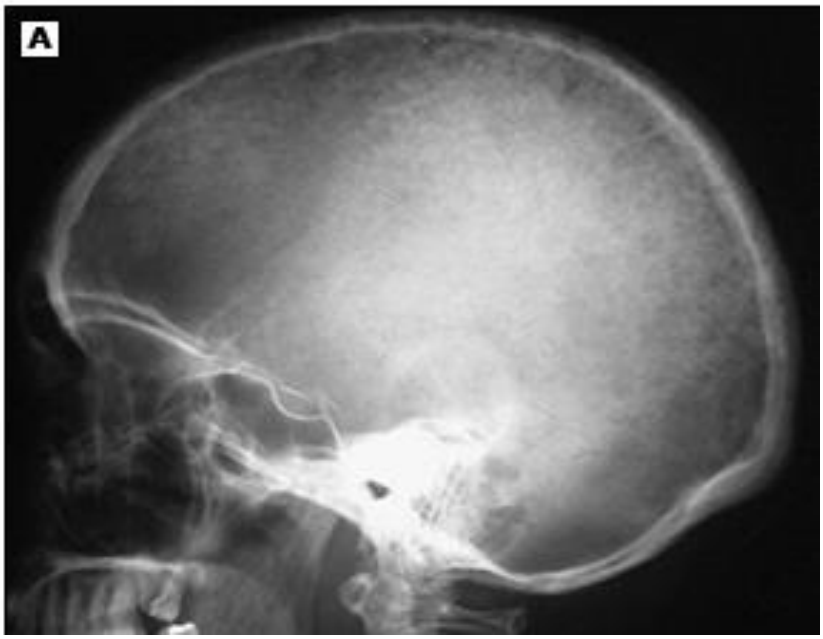

Fig3- Skull radiograph shows the typical "salt and pepper" appearance caused by osteitis fibrosa cystica.

Dual-energy X-ray absorp-tiometry revealed osteopenia: wrist (T score: −1.9) and lumbar spine (T score: −1.3). Jaw X-ray was revealed no areas of bone rarefaction which would have put the patient to high risk of developing osteonecrosis.

The operation day fixed and did on 15/04/2021, no postoperative complications. Few days later, the patient was reexamined and she was still suffering from the same complains. Series of serum calcium and PTH levels were unchanged (calcium 13.6 mg/dL, PTH 765.7), proved erratic and showed an upward trend over the preoperative levels. The patient denied any improvement.
Histopathological report of parathyroidiectomy revealed nodular hyperplasia of the two excised parathyroid glands.

Long-term clinical and biochemical follow-up was scheduled, the patient returned to her city.
After an open discussion with the operating surgeon and review of operation procedure (he removed only 2 hypertrophied gland, and the remaining 2 gland were normal shape and size and not excised). After revision of post-operative laboratory and histopathological results, it was conclude that the cause of her hyperparathyroidism was most likely a diffuse hyper-parathyroidism.
Regarding the severity of metabolic symptoms and post-operative conclusion, it was decided that a second surgery is the only curable possibility. Few days later and after the patient consent, a second parathyroidiectomy was done on 06/07/2021 with hope to excise the remnant two parathyroid glands.
No postoperative complications were documented.
Few days later, the patient came with same complains and no improvement noted. Post second operation laboratory results (calcium 1272 mg/dL, PTH 1070 pg/ml), reveals still high level of her calcium and PTH which could be related to manipulation during the operation.

After receiving the terrible histopathology result (The three specimens show thyroid tissue with nodular hyperplasia and absence of any parathyroid tissue). Due to the lack of facility for 99m technetium-sestamibi (SESTAMIBI) scintigraphy in our country and difficulty to do it abroad, our best diagnostic option available was a repeated another parathyroid ultrasound by another expert radiologist which reported that "right sided lateral to and infero-lateral to the lower pole of the right thyroid , and just behind the right common carotid artery origin 2X1.5 cm hypoechoeic solid nodule with medial sided feeding vessels, its long axis is along axis of the neck. Ultrasound findings are highly suggestive of right parathyroid adenoma".

After a discussion with this radiologist and another expert surgeon and after a consent of patient and her husband, a third operation was done on 21/08/2021 with aid of intraoperative endoscopy (no facility of intra-operative PTH assessment). With intra-operative ultrasound exploration, a right side parathyroid adenoma was excised along with accidental suprasternal soft tissue mass excision with morphological features compatible with thymic hyperplasia. Post-operative hungry bone syndrome (calcium 7.2 mg/dL, PTH <1.2 ng/ml) was documented treated by high calcium supplementation, no other significant postoperative complications.

III) Discussion

After initial parathyroidectomy, some patients develop persistent or recurrent disease. This operation failure should be confirmed biochemically and the indications for operation considered [2,7]. Because the risks of complications, these operations should be performed by experienced surgeons with reoperative neck surgery [8]. Several studies have demonstrated higher cure rates, fewer complications, lower cost, and shorter length of stay when parathyroid surgery is performed by high-volume surgeons and in high-volume centers It is the authors' recommendation that parathyroidectomy be performed by surgeons who perform no fewer than 10 procedures and ideally ≥50 procedures per year[2,60-62]..

It is generally recommended that two concordant imaging studies for localization be obtained prior to re-exploration. Ultrasound-guided fine needle aspiration of a suspected gland(s) with both histology and parathyroid hormone (PTH) assay could be helpful in localization of affected gland [7]..

The best candidate for re-do parathyroid surgery is a patient who (A) has severe or symptomatic primary hyperparathyroidism (serum calcium >11.5 mg/dl). (B) has a clear target on imaging and those with symptoms such as kidney stones, loss of kidney function, and osteoporosis have a strong motivation to pursue additional surgery.[9,10]

Ectopic thyroid tissue, thyroid nodules, and lymph nodes can easily resemble an enlarged parathyroid gland, especially in a reoperative case or when the patient has concomitant thyroiditis [66]. If the second parathyroid gland ipsilateral to the first is enlarged, the diagnosis of multigland disease is made, and multigland resection should be performed after a four-gland exploration [2].

In patients with four-gland hyperplasia, all but a portion of one enlarged gland is removed, leaving a well-vascularized parathyroid remnant of 50 to 100 mg size. This is referred to as a subtotal or three-and-half-gland resection. [76-74-68-67]. Sometimes, all the parathyroid glands cannot be identified readily. A systematic search is performed based on the knowledge of the path of descent of superior and inferior parathyroid glands.

A) Steps suggested to avoid operative failure

1- The operative report should detail the findings and events of parathyroidectomy .

2- The excised gland can be photographed or the surgeon can include a drawing of the operative findings in the written operative report .[63]

3- Preoperative localization is an integral part of a focused parathyroid exploration .

4- Commonly used localization studies include:

- **i.** cervical ultrasound, sestamibi scan.
- **ii.** Multiphase contrast-enhanced computed tomography (CT) of the neck (four-dimensional CT) .

5- Intraoperative parathyroid hormone (IOPTH) monitoring provides real-time confirmation of surgical cure [94]. The use of IOPTH is suggested to avoid high operative failure rates .[2]

6- IOPTH monitoring takes advantage of the short plasma half-life of PTH (three to five minutes) and a rapid assay that produces measurements while the patient is still in the operating room [34,95-97]. A baseline PTH value is obtained at the start of the procedure, prior to skin incision. PTH levels are then measured following removal of the suspected adenoma [71]. A reduction of at least 50 % in PTH level from the baseline is an accepted standard for intraoperative confirmation of success [2,98,99 100،]

7- One to two weeks postoperatively, patients should be seen to review pathology and obtain a baseline postoperative biochemical assessment.

8- At six months postoperatively, patients should have a repeat clinic visit with biochemical assessment .[2,113]

9- At six months to one year following documented cure, a follow-up visit along with a repeat biochemical assessment and a comparative bone mineral density study is suggested [2,114].

Failure to achieve durable cure of hypercalcemia is the most common complication of parathyroid surgery (reported at rates of 1 to 5 %).

The classic calcium nadir occurs within the first 24 to 48 hours after a parathyroidectomy, and a serum PTH value can be obtained on the first postoperative day prior to discharge[117].

The success rate of initial parathyroid surgery by an expert surgeon is about 98%. [30,40,120-121].

The success rate of re-do parathyroid surgery by an expert surgeon is 80-95%.

Re-do parathyroid surgery is risky. In experienced hands, the risk of permanent hoarseness (recurrent laryngeal nerve injury) during initial parathyroid surgery should be less than 1 in 200. In re-do parathyroid surgery, the risk is 1-3%[122-124-125].

In most reoperations for persistent or recurrent PHPT, the hyperfunctional parathyroid gland is identified in a usual and expected anatomic location.

The cure rate of reoperations may be improved using intraoperative parathyroid hormone monitoring to confirm excision of all hyperfunctioning tissue and, in some cases, to guide laterality of dissection [126-127-128].

B) Causes of recurrent hyperparathyroidism

1- Dormant (sleeping) second parathyroid adenoma, also known as subordinate adenoma.
2- Missed parathyroid hyperplasia.
3- Incomplete removal of a single parathyroid adenoma.
4- Parathyromatosis occurs when the initial surgeon breaks open the capsule of a parathyroid adenoma, causing abnormal parathyroid cells to spill out and seed the nearby soft tissues of the neck.
5- Parathyroid carcinoma.

Planning for re-do parathyroid surgery involves a combination of detective work (analysing what was done before), routinely request all prior operation reports, lab reports, pathology reports, and imaging reports, pathology slides for re-analysis.

IV) Conclusion:

Reoperation is technically challenging with higher rates of morbidity and higher incidences of recurrent laryngeal nerve (RLN) injury and permanent hypoparathyroidism as well as higher rates of failure to cure. Thus, indications for reoperations are more stringent than for initial surgery. Persistent or recurrent post-hyperparathyroidism disease may be the result of supernumerary glands, or unrecognized multigland disease but the leading cause is surgeon inexperience.

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