A RARE CASE OF PARATHYROID CARCINOMA MANIFESTING AS RECURRENT NEPHROLITHIASIS

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ABSTRACT

OBJECTIVES: To present a very rare case of Primary Parathyroid Carcinoma in a 54 year old female

: To discuss the clinical findings and management of Primary Parathyroid Carcinoma

METHODS:

Study Design: Case Report

Setting: Tertiary Hospital

Patient: One

RESULTS: A 54 year old female presented with a 3-year history of recurrent nephrolithiasis despite several shock wave lithotripsy. She had persistent hypercalcemia and parathyroid hormone level was noted to be elevated. Neck ultrasound showed a hypoechoic solid nodule measuring approximately 1.7x1.6cm in the lateral inferoposterior aspect of the left thyroid lobe. Parathyroid scintigraphy revealed a focal uptake on the left lower thyroidal bed. Patient underwent inferior parathyroidectomy, left with subtotal thyroidectomy, left and isthmusectomy Frozen section reported a parathyroid tumor and the final histopathologic results revealed a parathyroid carcinoma.

CONCLUSION: A very rare case of parathyroid carcinoma is presented, manifesting with recurrent nephrolithiasis. Elevated serum calcium and intact parathyroid hormone (iPTH) confirm a primary hyperparathyroid problem. Neck ultrasound and parathyroid scintigraphy help in the localization of a parathyroid tumor. Only final histopathologic result can confirm the diagnosis of parathyroid carcinoma. Complete surgical excision is the treatment of choice and offers a good prognosis.

KEYWORDS: Parathyroid Carcinoma, Primary Hyperparathyroidism

Kidney stone formation or nephrolithiasis is a condition brought about by many factors such as low daily urine volume; saturation of the urine with calcium, oxalate, calcium phosphate, uric acid or cystine, acidic urine; and bacterial infection[1]. The risk of nephrolithiasis is increased by certain medical conditions, including primary hyperparathyroidism, obesity, diabetes, gout, intestinal malabsorption, and anatomical abnormalities[2].

The majority of patients with nephrolithiasis have calcium-containing stones. Therefore, certain conditions that causes increase delivery of calcium to the kidney increases the risk for stone formation. The parathyroid gland is an endocrine organ that secretes parathyroid hormone (PTH) that regulates calcium balance in the body. In hyperparathyroidism, the serum PTH level is inappropriately elevated and the net effect is a rise in the serum calcium concentration leading to kidney stone formation[3].

Primary hyperparathyroidism is the unregulated overproduction of parathyroid hormone (PTH) resulting in abnormal calcium homeostasis secondary to an autonomous hyperfunctioning parathyroid tumor [4]. Less than 1% of urinary stone formers have primary hyperparathyroidism [3]. Hypercalcemia associated with elevated intact parathyroid hormone (iPTH) indicates a primary hyperparathyroidism. Primary hyperparathyroidism, while uncommon, can be benign or malignant.

Benign adenoma is the most common benign tumor of the parathyroid gland. Parathyroid carcinoma is a rare endocrine malignancy and it is also considered as an uncommon cause of PTH-dependent hypercalcemia. A systematic literature review of 22,225 cases of primary hyperparathyroidism reported between 1995 and 2003 revealed that parathyroid carcinoma accounted for only 0.74 percent of the cases [5]. Among all cancers, it has a prevalence of 0.005%, therefore, it is considered as the least common endocrine malignancy. Parathyroid carcinoma typically occurs among those age 40s to mid-50s. It may occur as a primary event or as part of a syndrome e.g. hyperparathyroidism-jaw tumor (HPT-JT) syndrome, multiple endocrine neoplasia types 1 and 2A, and familial hypocalciuric hypercalcemia[6].

There are no published local data on the incidence and prevalence of Primary Parathyroid Carcinoma.

It is the objective of this paper to present a case of a 54 year old female with a very rare case of a primary parathyroid carcinoma and discuss the clinical findings and appropriate management for this case.

CASE REPORT

A 54-year old female consulted due to hypogastric pain radiating to the flank. History started 3 years prior to admission, when patient experienced frequent hypogastric pain radiating to the flank area and burning sensation during urination. She occasionally experienced joint stiffness of both her hands but

with no evident swelling of her joints and occasional easy fatigability. There was no dyspnea, dysphagia, change in voice quality, fever, weight change and bowel habit changes. A consult with her private physician revealed that she had nephrolithiasis and she was advised to undergo shock wave lithotripsy. She would experience the same symptoms and she would undergo the same procedure three more times because of the recurrent nephrolithiasis. She had no other comorbid conditions. She is not taking any calcium supplements. Family history, personal and social history was unremarkable.

One year prior to consult, because of the recurrence of the above symptoms, she was advised urinary stent placement. On medical clearance prior to the procedure, routine serum electrolytes noted hypercalcemia which was persistent on repeated examinations (2.89-3.40mmol/L). Further laboratory tests were requested at that time. Baseline creatinine and BUN was within normal range. Baseline Thyroid function test showed normal results. However, parathyroid hormone (iPTH) was markedly elevated to 33.54 pmol/L.

Neck ultrasound showed an enlarged isthmus measuring 1cm in AP diameter and a hypoechoic solid nodule measuring approximately 1.7x1.6cm in the lateral inferoposterior aspect of the left thyroid lobe wherein a parathyroid etiology is considered. Parathyroid scintigraphy revealed a focal uptake on the left lower thyroidal bed.

Upon physical examination of the patient, multiple hypopigmented patches were distributed all over her body because of Vitiligo. There was no palpable neck mass or lymphadenopathies *(See Appendix A, Fig 1*). The rest of the ENT examination was unremarkable.

Admitting diagnosis was recurrent nephrolithiasis secondary to chronic hypercalcemia secondary to a primary hyperparathyroidism.

The patient underwent exploration of the neck, with possible excision of parathyroid tumor, with frozen section biopsy. Intraoperative findings *(See Appendix A, Fig 2 a-b*) revealed that the left thyroid gland is enlarged, with an approximately 2x2cm firm, dark, irregular nodular mass, located at the inferior pole. There is an approximately 1x1cm smooth, firm nodule at the inferior part of the thyroid isthmus. The right thyroid is grossly normal. Excision of the left thyroid mass was done to include the lower third and middle third of the left thyroid lobe. The whole isthmus including the nodule was excised. The specimen was sent for frozen section and revealed parathyroid tumor, left and benign thyroid nodule, isthmus.

Post-operatively, the serum calcium of the patient was closely monitored every 6 hours. After surgery, it showed a decrease from 3.7 to 2.10mmol/L *(See Appendix B, Fig 1*). Oral calcium supplementation was started. Patient only experienced mild symptoms of numbness of fingers which disappeared after 24 hours. Oral calcium supplementation was started on the first postoperative day and

patient was discharged improved on the fourth postoperative day. Regular follow-up of the patient was unremarkable.

Histopathologic results *(See Appendix A, Fig 3 a-d*) showed cells that are mostly in solid sheets with trabecular pattern and band forming fibrosis in some areas. Some follicles are lined by oncocytic cells and there is note of vascular invasion of the tumor.

Final histopathologic diagnosis reported Parathyroid Carcinoma.

DISCUSSION

Primary hyperparathyroidism is the unregulated overproduction of parathyroid hormone (PTH) resulting in abnormal calcium homeostasis. This is usually secondary to an autonomous hyperfunctioning parathyroid tumor. Secondary hyperparathyroidism on the other hand is the overproduction of parathyroid hormone secondary to a chronic abnormal stimulus for its production. Typically, this is due to chronic renal failure[4].

In primary hyperparathyroidism, the most commonly affected organs are the renal and skeletal systems. The classic, specific symptoms (i.e., bone disease, renal stones, and hypercalcemic crisis) represent obvious manifestations of the disease. Greater than 50% of patients with hyperparathyroidism develop renal symptoms manifested by nephrolithiasis and nephrocalcinosis. Nephrolithiasis is a condition wherein there is formation of stones within the urinary tract, on the other hand, nephrocalcinosis is characterized by the deposition of calcium in the kidney parenchyma and tubules[7]. The patient presented with hypogastric pain radiating to the flank area, burning sensation upon urination and was diagnosed with recurrent nephrolithiasis, for which she underwent repeated lithotripsy procedures. In primary hyperparathyroidism, nonspecific symptoms include malaise, fatigue, depression and other psychiatric symptoms, sleep disturbance, weight loss, abdominal pains, constipation, vague musculoskeletal pains in the extremities, and muscular weakness should be elicited[7]. The patient only complained of occasional joint stiffness and easy fatigability.

On physical examination, this patient did not present any palpable neck mass or lymphadenopathies suggestive of benign parathyroid pathology rather than parathyroid carcinoma because according to *DeVita* et. al., it is extremely unusual for patients with benign parathyroid lesions to have palpable abnormalities in the neck. The same author reported that a malignant pathology will present with palpable neck mass in 22-50% of cases[8].

On patient's routine electrolyte examination, serum calcium was incidentally noted to be elevated and repeated tests showed persistent hypercalcemia. Hypercalcemia may be attributed to medications, familial hypocalciuric hypercalcemia, but most commonly in primary hyperparathyroidism and malignancy [9]. Because of the persistent hypercalcemia, further tests such as parathyroid hormone level determination are needed to confirm the

diagnosis of primary hyperparathyroidism. Indeed, in this patient, intact parathyroid hormone was noted to be elevated which confirmed the diagnosis.

Is the recurrent nephrolithiasis brought about by primary hyperparathyroidism? The physiologic calcium metabolism is primarily regulated by the parathyroid gland. The main effects of parathyroid hormone is to increase the concentration of plasma calcium by increasing the release of calcium and phosphate from bone matrix, increasing calcium reabsorption by the kidney, and increasing renal production of 1,25-dihydroxyvitamin D-3 (calcitriol), which increases intestinal absorption of calcium [4]. The overproduction of parathyroid hormone results in the elevation of serum calcium, and in turn promotes calcium deposition in various organs. Specifically, calcium deposits in the kidneys lead to nephrocalcinosis and nephrolithiasis. The calcium level of this patient was noted to be persistently higher than normal in several occasions. The elevated serum calcium in this patient leads us to suspect a parathyroid pathology which was eventually confirmed by elevated parathyroid hormone level. The presence of elvated calcium and parathyoid hormone is diagnostic of primary hyperparathyoidism. Therefore, in this patient, the recurrent nephrolithiasis was brought about by primary hyperparathyroidism.

The increase in secretion of parathyroid hormone in primary hyperparathyroidism is the result of the autonomous hyperfunctioning of one or more of the parathyroid glands. This may be a benign parathyroid adenoma or parathyroid carcinoma[10].

There are diagnostic tests like neck ultrasound and parathyroid scintigraphy that may help detect parathyroid gland abnormality. Neck ultrasound and nuclear medicine studies such as technetium-99m sestamibi and parathyroid scintigraphy have been useful in localizing hyperfunctional parathyroid masses as well as parathyroid carcinoma. Normal parathyroid glands are rarely visualized by ultrasonography, because of their small size and insufficient acoustic difference compared to adjacent thyroid tissue. However, parathyroid tumors exhibit a relatively hypoechogenic pattern. It is usually well-circumscribed, tend to be solid and homogenously hypoechoic relative to echogenic thyroid tissue [11]. The ultrasound appearance of parathyroid malignancy on the other hand is a hypoechoic soft tissue mass with irregular, poorly defined border with sign of invasion of adjacent structures [5].

The neck ultrasound findings in this patient revealed a hypoechoic solid nodule in the lateral inferoposterior aspect of the left thyroid lobe, suspecting a parathyroid origin. A parathyroid scintigraphy of this patient showed focal uptake on the same area which strongly supports the impression of a parathyroid pathology. In this patient, ultrasound and scintigraphy findings suspected only a parathyroid tumor but cannot assess whether benign or malignant parathyroid tumor.

There are some biochemical parameters that may differentiate benign from

malignant parathyroid tumor. The degree of hypercalcemia and hyperparathyroidism are often more pronounced in parathyroid carcinoma. Calcium levels above 14 mg/dL (N.V. 8.5-9.9mg/dL) are more common in parathyroid carcinoma, as compared to elevations of 1-2mg/dL among other etiologies of primary hyperparathyroidism [8]. In this patient, serum calcium levels range from 2.89 to 3.40mmol/L, consistent with a benign parathyroid tumor rather than a carcinoma.

Up to 14% of patients with parathyroid carcinoma will present with hypercalcemic crisis manifested with depressed level of consciousness, dehydration and extreme hypercalcemia[4]. Our patient did not manifest any of these problems.

According to *De Vita* et.al., the intraoperative findings of a parathyroid carcinoma typically appears to be tan to grayish, hard, lobulated, and fibrous in texture as compared to a parathyroid adenoma which is red or brown, soft, and free of attachment to its surrounding structures. A larger gland size of >3cm has more tendency to be malignant and it has a predilection to occur in the inferior parathyroid gland [8]. In this patient, the only gross findings which may lead to suspect malignancy is the firm, dark, irregular nodular mass that was closely adherent at the inferior thyroid pole. While the mass was initially thought to be a thyroid mass intraoperatively, the pathologist reported it as parathyroid tumor by frozen section. Unexpectedly, the final histopathologic diagnosis was parathyroid carcinoma. According to Shane, if one or all of the malignant intraoperative findings may be absent, examination of frozen sections is of little value in distinguishing benign from malignant disease [12].

The management of primary hyperparathyroidism is excision of the autonomous hyperfunctioning parathyroid gland. If found to be malignant, wide tumor excision should be done. Parathyroid carcinomas are associated with an indolent, slowly progressive course [13]. The most important factor that would affect prognosis is the completeness of tumor resection. In this patient, the parathyroid tumor was completely excised en bloc with adequate margin of safety. According to *Kleinpeter*, et. al., patients who undergo complete en-bloc tumor resection can have survival rates as high as 90% at 5 years and 67% at 10 years[19].

Other treatment options like radiation therapy for parathyroid carcinoma has not been demonstrated to have a significant effect in either the neck or at sites of distant metastases[19].

Histologic diagnosis of parathyroid carcinoma is suggested by the presence of intraoperative features of local invasion and the diagnosis is confirmed by the World Health Organization histopathological criteria for parathyroid carcinoma. These include the presence of vascular invasion, perineural space invasion, capsular penetration with growth into adjacent tissues and/or metastasis [14]. A meta-analysis by Obara et. al. stated that the finding of fibrous bands was the most sensitive histopathological feature, whereas trabecular

growth pattern, capsular invasion and vascular invasion offers the highest specificity[17]. In this patient's microscopic findings of trabecular pattern, fibrous bands and vascular invasion confirmed the diagnosis of parathyroid carcinoma.

Post-operatively, serum calcium level should be monitored regularly with standby IV calcium infusion, when clinical signs of hypocalcemia sets in. This phenomenon of hypocalcemia after surgical removal of the hyperfunctioning parathyroid tumor can be explained by the sudden drop in the serum level of parathyroid hormone and subsequent drop of serum calcium. This phenomenon is called Hungry bone syndrome, wherein calcium is reabsorbed back toward the bone matrix resulting in decrease level of calcium in the blood. This is a temporary event and stabilizes usually after 24 hours[12]. The patient calcium level was regularly monitored postoperatively. It showed decrease from 3.7 to 2.10mmol/L. The patient only manifested temporary mild numbness of her fingers. Oral calcium supplementation was started on the first postoperative day and patient was discharged improved on the fourth postoperative day. Regular follow-up of the patient was unremarkable.

In conclusion, a 54 year old female presented with a very rare case of parathyroid carcinoma, manifesting with recurrent nephrolithiasis. Elevated serum calcium and intact parathyroid hormone (iPTH) confirm a primary hyperparathyroid problem. Neck ultrasound and parathyroid scintigraphy help in the localization of a parathyroid tumor. Only formal histopathologic procedure can definitely confirm the diagnosis of parathyroid carcinoma. Review of literature states that surgery is still the treatment of choice for parathyroid malignancy and offer good prognosis for the patient.

It is recommended that further studies be done to increase awareness among physicians that for patients with recurrent nephrolithiasis, parathyroid pathology should also be considered.

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ILLUSTRATIONS

APPENDIX A

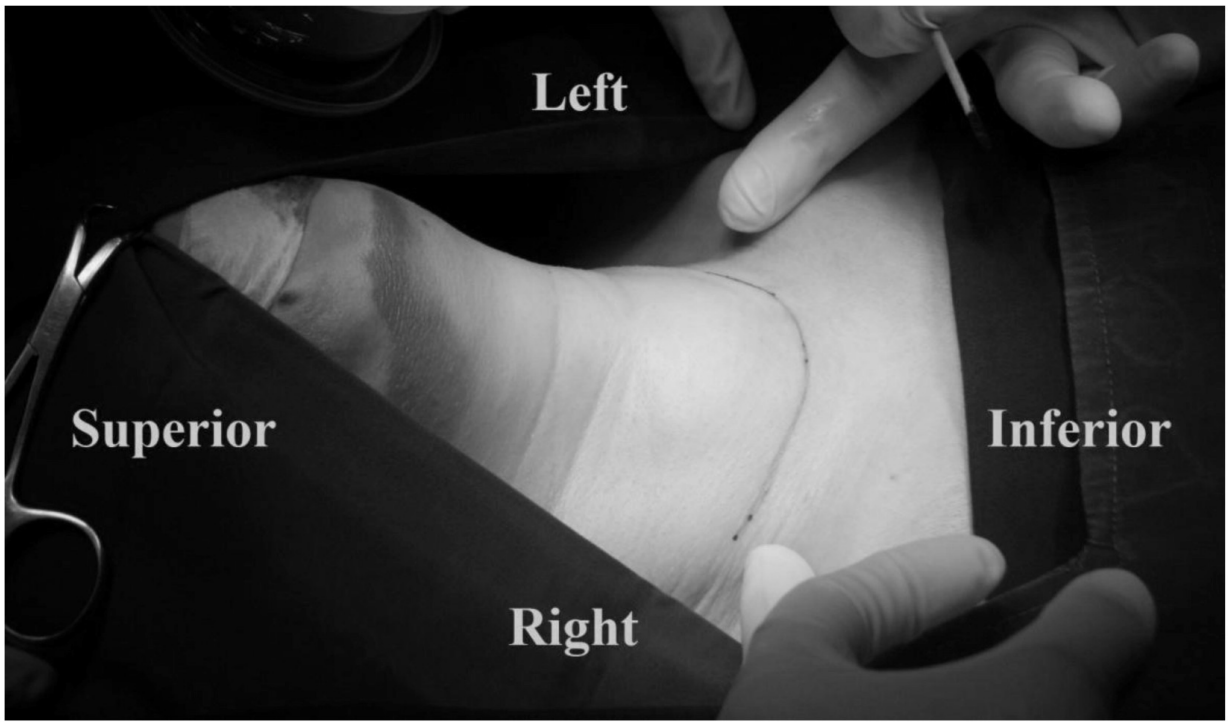
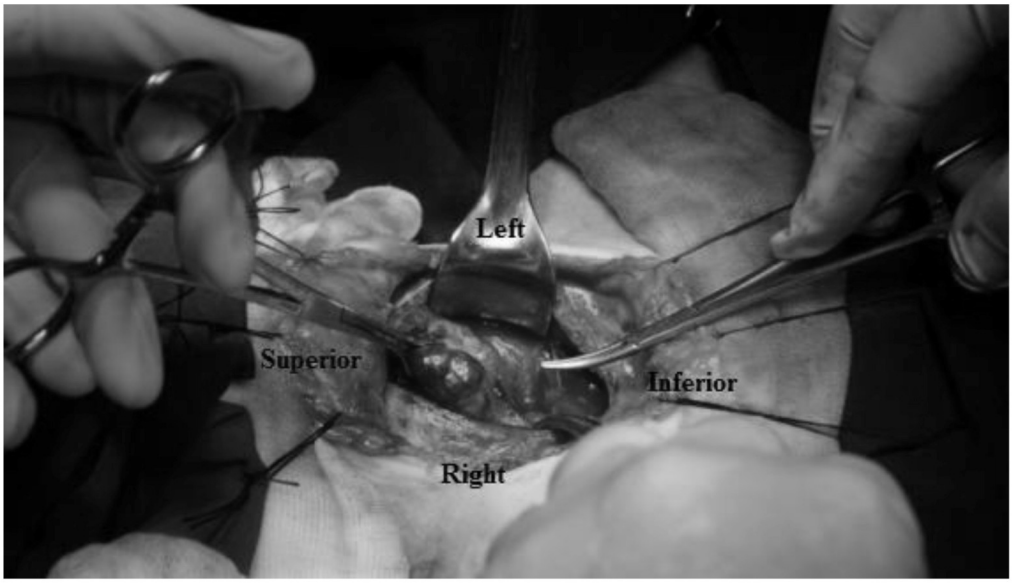
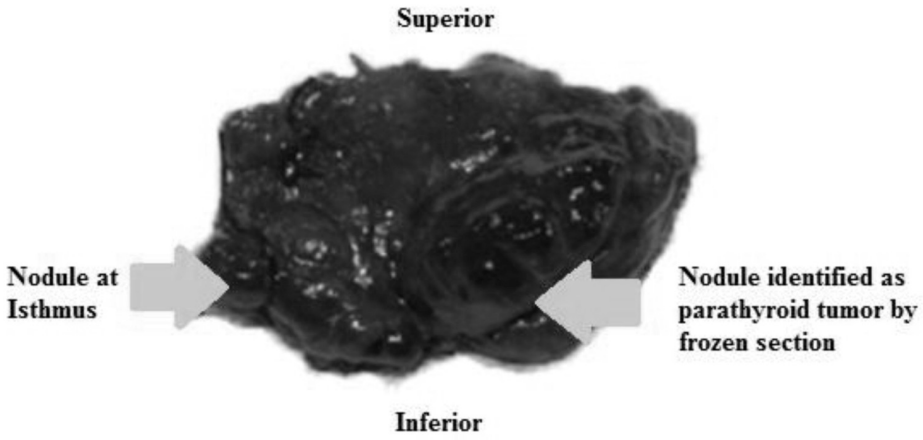


Figure 1. The patient had no palpable neck mass or lymphadenopathies



(a)



(b)

Figure 2. (a) Intraoperative findings (left thyroid lobe is freed and retracted from its bed) showed that the left thyroid gland is enlarged, with an approximately 2x2cm firm, dark, irregular nodular mass, located at the inferior pole. There is an approximately 1x1cm smooth, firm nodule at the inferior part of the thyroid isthmus. The right thyroid is grossly normal. (b) Specimen

APPENDIX A

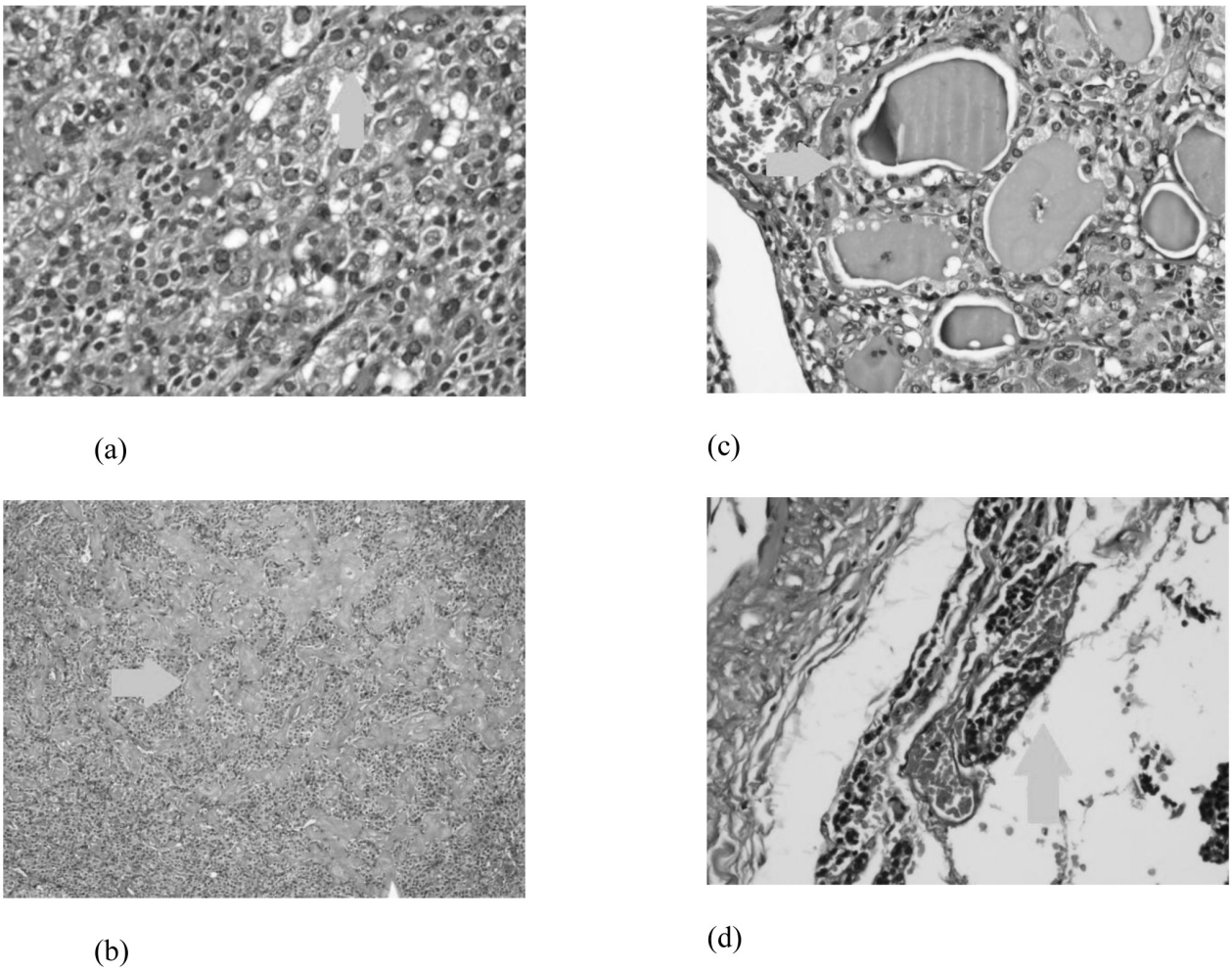
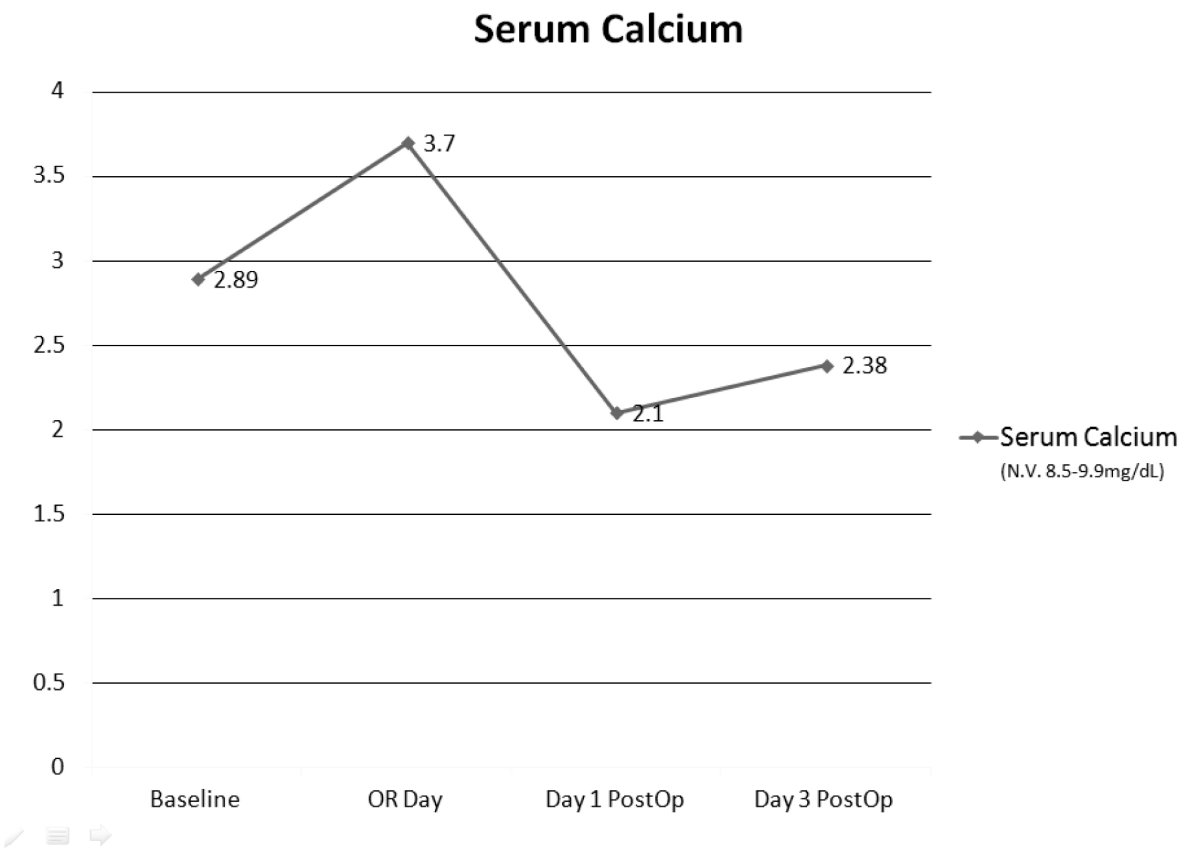


Figure 3. Microscopic appearance of parathyroid carcinoma as seen in the patient. (a) Cells mostly in solid sheets with trabecular pattern (hematoxylin and eosin stain (H&E); magnification 200x). (b) Band forming fibrosis (H&E; 20x), (c) Follicles lined by oncocytic cells (H&E; 200x), (d) Note of vascular invasion of the tumor (H&E; 200x)

APPENDIX B



Graph. 1. After surgery, serum calcium of the patient was monitored every 6 hours