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CASE REPORT

Parathyroid Adenoma with Macrofollicular Growth Pattern: A Rare Histopathological Entity

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Abstract

The majority of parathyroid adenomas can be localized preoperatively using various imaging techniques. The success rate of focused parathyroidectomy exceeds 95% when performed by an experienced surgeon. Here, we report an apparent failure of focused right inferior parathyroidectomy performed for a preoperatively detected parathyroid adenoma. This misinterpretation arose due to macrofollicular growth pattern of the resected parathyroid adenoma, which mimicked thyroid tissue. The patient subsequently underwent re-exploration, including intraoperative ultrasound, which revealed that the culprit gland had, in fact, been successfully removed during the initial surgery. This finding was also supported by a significant decrease in the intraoperative parathyroid hormone level, as compared to the pre-operative level. This case highlights the rare macrofollicular histology of parathyroid adenoma and underscores the importance of a multidisciplinary team in successfully treating the condition.

Key words: parathyroid adenoma, macrofollicular growth pattern, parathyroidectomy

INTRODUCTION

Hyperfunctioning parathyroid adenoma is the most common cause of primary hyperparathyroidism (PHPT).[1] Classically, PHPT presents with nonspecific features of hypercalcemia such as vague abdominal pain, neuromuscular weakness, bone disease, osteoporosis, neuropsychiatric manifestations, recurrent nephrolithiasis, or rarely, pancreatitis. Recently, with the increasing use of biochemical tests and ultrasonography, the diagnosis of asymptomatic disease is increasing.[1]

We discuss a 29-year-old female who was diagnosed to have PHPT (high serum calcium with raised intact parathyroid hormone (iPTH), while being evaluated for nephrolithiasis. Preoperative imaging studies localized a single right inferior parathyroid adenoma. Despite preoperative diagnosis and localization, the tissue diagnosis of parathyroid adenoma could only be made after two surgical attempts. In this case, the frozen section of the excised tissue exhibited macrofollicular growth pattern, morphologically resembling normal thyroid parenchyma. As a result, the tissue diagnosis was missed, leading to a repeat neck exploration to identify the culprit gland.

CASE

A 29-year-old female presented with sudden onset flank pain radiating to the groin at a local hospital seven months ago. There was no history of fever, polyuria, or dysuria. No neuropsychiatric symptoms, or history of fractures or bone pains were noted. Ultrasonography of the abdomen revealed bilateral renal calculi, measuring 14 mm and 16 mm. Computed tomography (CT) urography confirmed bilateral renal calculi with dilated right pelvicalyceal system. Blood investigations including complete blood counts and renal function tests were normal except for raised serum calcium levels [10.8 mg/dL (normal range: 8.4-10.2 mg/dL)]. On further evaluation, iPTH level was found to be markedly elevated (213 pg/mL, normal range: 13.6-85.6 pg/mL) and serum 25-hydroxy vitamin D level was not deficient (28.3 ng/dl, normal range: 10 – 44 ng/dl), suggestive of PHPT. Subsequently, the patient was referred to our institution for further management.

Parathyroid localization with an initial neck ultrasound was done which revealed a hypoechoic lesion inferior to the right lobe of thyroid measuring 9 × 6 mm, suggestive of right inferior parathyroid adenoma. Subsequently, ^{99m}Tc sestamibi scintigraphy was performed, which was

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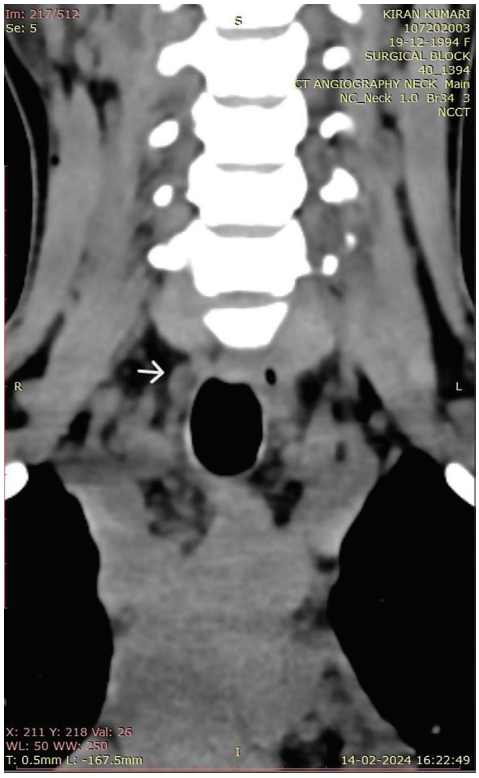

Figure 1. 4D-CT showing right inferior parathyroid adenoma *(white arrow)* immediately below the lower pole of right thyroid lobe.

inconclusive. As there was discordance between the above two imaging findings, four-dimensional CT (4D-CT) neck was done which showed a well circumscribed nodular soft tissue lesion lying posterior to the lower pole of right lobe of thyroid gland in paratracheal location, measuring 10 × 7 × 13 mm in size. There was enhancement in the arterial phase and washout during delayed phase suggestive of right inferior parathyroid adenoma (Figure 1).

As it was a pre-operatively localized parathyroid adenoma involving a single gland, focused right inferior parathyroidectomy was planned. During surgery, a suspicious lesion immediately below the right inferior thyroid artery was found and excised along with surrounding pad of fat and sent for frozen section. Intraoperative iPTH and serum calcium were also sent. The frozen section report indicated presence of tissue with macrofollicular growth pattern suggestive of thyroid tissue, without any evidence of parathyroid adenoma (Figure 2). In view of the possibility of failed surgery, re-exploration was done. However, there was no abnormal lymphoid or fatty tissue in the suspected area. To optimize localization, an intraoperative ultrasound was performed by an experienced radiologist who also concluded absence of any suspicious tissue at the site of the right inferior parathyroid adenoma. The post-resection iPTH and calcium levels reflected a marked decline in iPTH levels to 5 pg/mL, and normalization of serum calcium to 9.4 mg/dL. Such findings pointed towards an evidence of successful removal of parathyroid adenoma during initial exploration and resection itself.

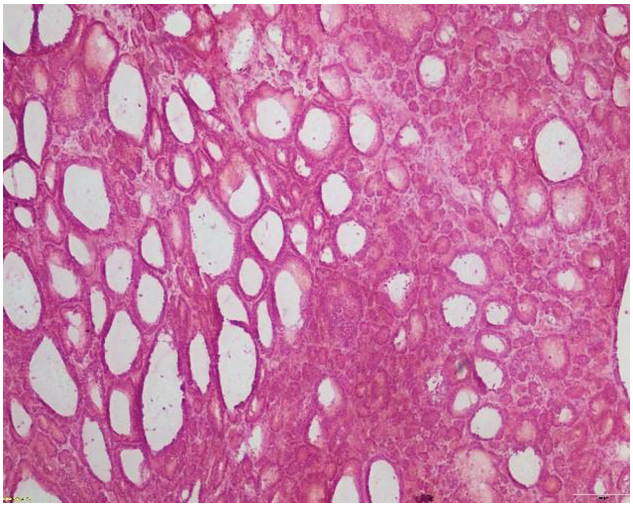

Figure 2. H&E-stained frozen section (40x) shows a lesion predominantly arranged in a follicular pattern.

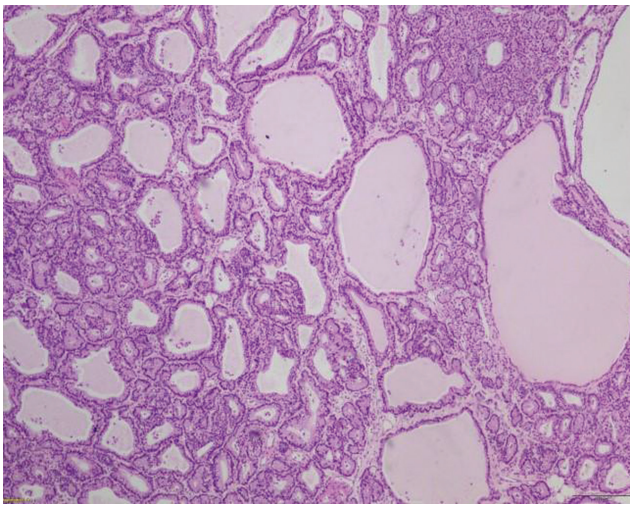

Figure 3. H&E-stained slide from a formalin-fixed, paraffin-embedded section shows a similar lesion predominantly arranged in a follicular pattern, with monomorphic nuclei and abundant clear cytoplasm (40x).

To resolve the enigma, the findings of re-exploration, intraoperative ultrasound and iPTH, and serum calcium were discussed with the pathologist. The frozen section slides of the surgery were reviewed again, and histopathology revealed an unusual morphology comprising of a tissue with monomorphic round nucleus and abundant clear cytoplasm having columnar appearance, arranged in comprehensive follicular pattern (Figure 2). The morphology of the parathyroid gland closely resembled that of the thyroid, leading to diagnostic uncertainty. Finally, histopathological report of formalin fixed paraffin embedded specimen confirmed parathyroid adenoma with macrofollicular growth pattern with adjacent normal parathyroid parenchyma (Figure 3). Immunohistochemistry was performed on formalin fixed paraffin embedded section and the cells were found to be immunopositive for parafibromin (Figure 4) and GATA 3. Cells were negative for TTF 1 and the Ki 67 index was less than 1 %.

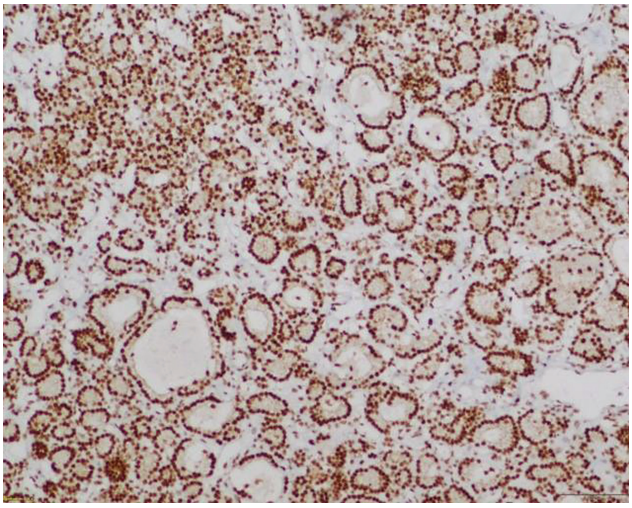

Figure 4. Immunohistochemical staining for parafibromin shows diffuse nuclear positivity (parafibromin IHC, 100x).

DISCUSSION

This case report highlights the challenges of distinguishing parathyroid gland lesions from thyroid lesions cytopathologically in a clinical setting. Our patient manifested with classical features of PHPT with right inferior parathyroid adenoma localized preoperatively by ultrasonography and 4D-CT. However, despite successful removal of the adenoma during the surgery, as confirmed by intraoperative biochemical findings, re-exploration had to be done in light of frozen section biopsy findings mimicking a follicular thyroid lesion.

Previous pathologic reports have highlighted the difficulty in differentiating parathyroid from thyroid lesions on fine needle aspiration cytology. However, combination of cytological features may point towards a parathyroid lesion rather than thyroid tissue as described by Kimberley et al.[2] Approximately 40% of the cases of parathyroid adenoma may exhibit microfollicular structure like that of a thyroid adenoma,[3] however, thyroid follicular lesions also have macrofocllicles.[2] In addition, intracytoplasmic fat vacuolation, high cellularity, small dark nuclei, bare nuclei, nuclear molding and overlapping are features more suggestive of parathyroid lesion.[2,4,5] The presence of predominant follicular structures in a parathyroid adenoma is an atypical finding which may unexpectedly challenge histopathological interpretation. In such cases, the absence of birefringent calcium oxalate crystals, and the presence of well-defined cell membranes can help in the differentiation from the thyroid tissue.[6] The documentation of such characteristics in real-time clinical practice is essential to prevent unnecessary delays in establishing an accurate diagnosis. These cytologic features, along with PTH immunoassay and/or immunostainings for GATA3 and parafibromin on cytologic specimens, aid in differentiating parathyroid from thyroid lesions.[7]

Only a handful of case reports in the past have described misdiagnosis of parathyroid adenoma as thyroid lesion in the clinical setting.[8-10] In a patient with neck mass and hypercalcemia, aspiration cytology findings of cohesive clusters of monomorphic hyperchromatic cells resembling follicular cells, and papillary formation and follicle-like arrangements suggested the diagnosis of papillary carcinoma of the thyroid. Finally, histopathologic examination of the excised mass revealed parathyroid adenoma.[9] In a report by Peterson et al, a 57-year-old female was conservatively managed for 8 years by repeated fine needle aspiration biopsy of a mildly suspicious thyroid nodule that showed atypical thyroid epithelial cells and the nodule was categorized as an atypical/follicular thyroid lesion Bethesda Class III. This thyroid nodule was not accurately diagnosed as parathyroid adenoma until the patient developed pathological hip fracture, with subsequent biochemical evaluation also suggestive of PHPT. Focused parathyroidectomy resulted in complete resolution of the symptoms in the patient.[10] Although follicular growth pattern has been reported in parathyroid adenomas, macrofollicular growth pattern of parathyroid tissue, as observed in our case, has not been documented in the literature.

CONCLUSION

The appropriate management of parathyroid adenoma requires close coordination among an experienced surgeon, pathologist, and radiologist. The role of biochemical investigations in both the preoperative diagnosis and intraoperative assessment for confirming successful gland removal is paramount. Lastly, challenges in histological diagnosis can be resolved through ancillary tests, including PTH immunoassay and immunostaining for GATA3, and parafibromin.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
RM: Conceptualization, Investigation, Writing – original draft preparation; **BKS:** Conceptualization, Investigation, Writing – original draft preparation; **AN:** Conceptualization, Writing – original draft preparation; **AK:** Conceptualization, Writing – review and editing; **DK:** Conceptualization, Writing – review and editing; **SS:** Conceptualization, Writing – review and editing; **VS:** Conceptualization, Writing – review and editing, Supervision.

Data Availability Statement
No datasets were generated or analyzed for this study.

Author Disclosure
The authors declared no conflict of interest.

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