Intravaginal parathyroid adenomas: Case report and literature review

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Abstract
Intravagal parathyroid adenomas remain an exceedingly rare diagnosis; however, their true incidence may be higher than currently known. It is important to keep intravagal sites within the list of potential ectopic locations of parathyroid adenomas.

Keywords
adenoma, hyperparathyroidism, intravagal, parathyroid, vagus nerve

1 | INTRODUCTION
During embryogenesis, parathyroid glands develop from the third and fourth pharyngeal pouches and descend to their respective destinations at the inferior and superior locations on the dorsum of the thyroid.1 A disruption in this migration can lead to ectopic parathyroid tissue anywhere along this path or within adjacent tissues. Ectopic parathyroid tissue is

Figure 1 A, Transverse CT demonstrating an ovoid heterogeneous mass with partial occlusion of the oropharynx. B, Sagittal T2-weighted magnetic resonance scan showing the anterior displacement of the carotid arteries due to the mass effect. C, Coronal T1-weighted magnetic resonance scan revealing the location of the mass and the effect on surrounding structures

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a well-recognized phenomenon and has been documented in locations from the carotid sheath to the middle mediastinum.\textsuperscript{2} It is important to recognize the potential for abnormally located parathyroid tissue as parathyroid adenomas are treated surgically.

While ectopic parathyroid adenomas have been well described, intravagal parathyroid adenomas are rare and have only been documented in the literature in 12 previous cases.\textsuperscript{3-10} Here, we describe the identification, management, and postsurgical outcomes of two additional cases of parathyroid adenomas within the vagus nerve.

\section*{HIGHLIGHTED CASES}

Patient 1 is a 52-year-old female who presented to clinic for evaluation of a neck mass and associated dysphonia, dysphagia, persistent cough, and left neck, ear, and jaw pain for three months. Physical examination revealed a bulging left tonsil displaced medially, and flexible laryngoscopy showed left true vocal fold paralysis. Her serum calcium level was 12.9 mg/dL. CT and MRI revealed a 2.3 cm parapharyngeal mass within the left carotid sheath displacing both the internal and external carotid arteries anteriorly.
Table 1: Compares the case details of two adults diagnosed with intravagal parathyroid adenomas at the University of Florida Shands Hospital compared to the case details of all additional documented intravagal parathyroid adenomas in the English literature.

| Author/Year | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|-------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Author y   | Dz 2019 (this study) | Dz 2019 (this study) | O’Neil et al 2019 | Daruwalla et al 2015 | Chan et al 2003 | Chan et al 2003 |
| Sex        | Female | Male | Male | Female | Female | Female |
| Age (y)    | 52 | 34 | 43 | 17 | - | - |
| Presenting symptoms | Dysphonia, dysphagia, left ear and jaw pain, cough | Fatigue, mild dysphagia, dysphonia | None | Fatigue, nephrolithiasis | - | - |

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| Presenting serum PTH | 134 | 121 | NA | 12.1 pmol/L | Elevated | Elevated |
| Presenting serum calcium | 12.9 mg/dL | 12 mg/dL | NA | 2.81 mmol/L | Elevated | Elevated |
| Imaging history | US, CT, MRI | US, CT, MRI, SS | US, CT, Dual tracer, SG | US, SS | US, SA | US, SA, SVS |
| Size of lesion | 5 x 3 cm | 0.8 x 0.6 x 0.4 cm | 14 mm | 7 mm | 13 x 8 x 7 mm | 6 x 5 x 2 mm |
| Location of lesion | Left VN above level of CB | Right VN at the CB | Left VN above level of CB | Left VN at level of CB | Left VN above level of CB | Right VN above level of CB |
| Approach | Transoral approach surgical resection | Skull base approach surgical resection | Level I-II selective neck dissection and surgical excision | Left-sided parathyroid exploration, left cervical thymectomy | Left oblique cervical approach resection | Right oblique cervical approach |
| Surgical Pathology | Hypercellular parathyroid adenoma | Hypercellular parathyroid adenoma | Hypercellular parathyroid adenoma | Parathyroid tissue | Hypercellular parathyroid adenoma | Hypercellular parathyroid adenoma |
| Post-op serum calcium | 8 mg/dL | (ionized) 1.45 mmol/L | Normalized | 2.31 pmol/L | normalized | normalized |
| Post-op symptoms | Left true vocal fold paralysis, left tongue deviation, Horner syndrome | None | Transient recurrent laryngeal nerve paresis | None | - | - |

Abbreviations: CB, carotid body; SA, selective angiography; SG, scintigraphy; SS, 99m Tc sestamibi scan; SVS, selective venous sampling; VN, vagus nerve.

*Pertechnetate/sestamibi subtraction.

(Figure 1). A CT-guided fine-needle aspiration was performed and was originally interpreted as thyroid tissue due to thin colloid with groups of follicular-type cells in the sample. Resection of the mass without capsule disruption was performed via a transoral approach and revealed a 5 x 3 cm mass, though unusually large surgical pathology confirmed a benign parathyroid adenoma without nuclear atypica, foci of necrosis, or increased mitotic activity. The mass was inferior to the skull base and superior to the carotid bifurcation. Her immediate postoperative calcium level was at 9.0 mg/dL. On postoperative day 3, mild ptosis and anisocoria were noted of the left eye as well as left-sided mydriasis, consistent with a mild Horner’s syndrome. Tongue protrusion had slight leftward deviation. She was discharged on postoperative day 5. Tongue weakness resolved by 1 month post-op, and Horner’s syndrome resolved...
| Patient 7 | Patient 8 | Patient 9 | Patient 10 | Patient 11 | Patient 12 | Patient 13 | Patient 14 |
|----------|-----------|-----------|------------|------------|------------|------------|------------|
| Chan et al 8 | Chan et al 8 | Pawlik et al 7 | Pawlik et al 7 | Buell et al 6 | Doppman et al 5 | Takimoto et al 4 | Reiling et al 3 |
| 2003 | 2003 | 1999 | 1999 | 1995 | 1994 | 1989 | 1972 |
| Female | Female | Male | Male | Female | Female | Female | Female |
| - | - | 48 | 43 | - | 40 | 79 | 55 |
| - | - | Fatigue, muscle cramps, weakness, bone pain | Nephrolithiasis, fatigue, forgetfulness, abdominal discomfort | - | Fatigue, muscle weakness, constipation, nausea | Enlarging left sided neck mass | - |
| Elevated | Elevated | 1000 pg/ml | 98 pg/ml | - | 74 pg/ml | 2.14 ng/ml | - |
| Elevated | Elevated | 11 mg/dl | 12.3 mg/dl | - | 2.5-3.12 mmol/l | 6.4 mEq/l | - |
| SA, SVS | CT, MRI, SG | CT, SS, SVS | Left neck US, SS, SVS | US, SA, MRI, SVS, CT, SG | US, MRI, CT, SG, arteriography, SVS | US, CT, SG | US, CT, SG |
| 12 x 8 x 8 mm | 20 x 8 x 6 mm | 1.0 x 1.2 cm | 1.0 x 1.4 cm | - | 1.2 x 0.8 cm | 1.7 x 2.5 cm | 0.5 x 0.8 cm |
| Right VN above level of CB | Left VN below level of CB | Left VN at level of CB | Left VN at level of CB | Right VN above level of CB | Right VN above level of CB | Left VN below level of CB | Right VN at level of CB |
| Right oblique cervical approach | Left oblique cervical approach | Left lateral cervical approach and excision | Left lateral cervical approach and excision | - | Anterolateral cervical approach and excision | - | Right lateral cervical approach and excision |
| Hypercellular parathyroid adenoma | Hypercellular parathyroid adenoma | Hypercellular parathyroid adenoma | Hypercellular parathyroid adenoma | Hypercellular parathyroid adenoma | Parathyroid adenoma with cystic degeneration | Hypercellular parathyroid adenoma |
| normalized | normalized | 9.7 mg/dl | 5.0 mg/dl | - | - | 5.6 mEq/l | normalized |
| - | - | None | Transient left vocal fold paresis | - | Transient hypocalcemia and transient recurrent laryngeal nerve palsy | Transient left recurrent laryngeal nerve palsy | - |

by 1 year. Left true vocal fold never regained function and was stable from its pretreatment state.

Patient 2 is a 34-year-old male with known hyperparathyroidism who presented to clinic for evaluation of persistent hypercalcemia. Three months prior, he underwent a left thyroid lobectomy and failed left parathyroid exploration after imaging showed growth of a left thyroid nodule. Surgical pathology revealed a 3 cm minimally invasive follicular thyroid carcinoma, a separate 1 mm focus of papillary thyroid carcinoma, and non-hypercellular superior and inferior left parathyroid glands. On presentation, he was found to have calcium at 12 mg/dL and had symptoms of fatigue, mild dysphagia, and dysphonia. Physical examination was unremarkable aside from his surgical scar. CT neck with contrast showed an enhancing nodule at the level of the right carotid bifurcation lying medial to the jugular vein and posterior to
the carotid artery near the skull base. The washout characteristics of this nodule were consistent with a parathyroid adenoma, and an MRI confirmed these findings (Figure 2). Nuclear medicine parathyroid scan using IV sestamibi revealed focal uptake in the right carotid sheath corresponding to this nodule (Figure 3). Resection was performed via a transcervical approach, and a mass measuring 0.8 × 0.6 × 0.4 cm was dissected out from the vagus sheath in toto. Frozen section was consistent with hypercellular parathyroid gland. Intraoperative PTH increased to 365 pg/mL further confirming the mass as parathyroid tissue. Postoperative PTH dropped to 27 pg/mL, and postoperative calcium normalized at 8.3 mg/dL. A completion thyroidectomy was also performed. The patient was discharged the next day with a weak voice but no other deficits. Three months later his vocal cord was paretic, but he had a strong voice.

3 | DISCUSSION

Intravagal parathyroid adenomas have only been reported 12 times in the literature. Lack et al (1988) suggested that the incidence may be higher than currently known. His study examined the vagus nerves of 32 deceased infants under 1-year-old and found that 6% contained parathyroid cells, confirmed by chromogranin and PTH staining. This finding demonstrates that there may be an impressive subset of the population that is living with asymptomatic ectopic parathyroid tissue within the vagus nerve. This unusual location of parathyroid tissue was postulated to arise due to the close embryologic origins of both the vagus nerve and the parathyroid glands.11

Both patients presented in this case series underwent different workups due to the differences in their presentations and relevant past medical histories. Patient 1 presented with symptoms due to mass effect and was worked up with a biopsy because of the unclear nature of the mass. It was removed via a careful transoral approach. Due to extensive dissection at the skull base, she had temporary cranial nerve deficits but recovered to baseline. This can certainly be expected with a transoral approach to the parapharyngeal space.12 Patient 2 underwent parathyroid-specific imaging as an ectopic parathyroid gland was expected. His approach was transcervical, and his only sequela was vocal cord paralysis, which is recovering well. Both Patient 1 and 2 normalized their calcium and PTH levels postoperatively. Though the workup and surgical approaches varied, they were both equally appropriate given the clinical presentation and location of the mass.

The current known cases of intravagal parathyroid adenomas (Table 1) follow a similar sex ratio trend to the true incidence of parathyroid adenomas. Particularly, the ratio of female to male in this series is 2.5:1, mirroring the 2:3:1 female-to-male ratio of primary hyperparathyroidism in the population.13 The average age at presentation is 45 years, and all patients present with hypercalcemia. Preoperative imaging studies included all possible modalities as intravagal adenomas are challenging to diagnose on imaging. Eight (57%) patients contained left-sided adenomas. There was a notable predominance of adenomas located above or at the carotid bifurcation (7 and 5, respectively) compared to only 2 found below the carotid bifurcation. The sizes of the lesions varied from 2 to 50 mm at greatest diameter. All patients were treated surgically, and surgical pathology was universally found to show hypercellular parathyroid tissue. Two (14%) developed hypocalcemia following the surgery. Four (28%) experienced postoperative transient laryngeal nerve palsies while Patient 1 in this study presented with vocal cord paralysis.

Single-gland parathyroid adenomas are the leading cause of primary hyperparathyroidism contributing to 80%-85% of cases.14 It is important to be able to localize the source of hyperparathyroidism prior to surgical intervention, though this proves to be challenging. Imaging modalities such as 4D CT scanning and SPECT scans can be useful in identifying an abnormally located parathyroid glands. O’Neil et al reported success in using a gamma probe intraoperatively to help identify an intravagal parathyroid adenoma.10 The use of a gamma probe intraoperatively as an additional tool to help identify parathyroid tissue was described by Norman et al who treated patients with IV Tc99 sestamibi prior to surgery and then used the probe to localize parathyroid tissue allowing for a more minimally invasive approach.15 The use of preoperative imaging and intraoperative localization may prove to aid in the identification of ectopic parathyroid adenomas.

Surgical approach for intravagal parathyroid adenoma is dependent on the location and size of the lesion. In the literature, the dominant approach is transcervical with 12 out of 14 (85.7%) patients, while transoral and skull-based approaches constituted 1 out of 14 (7.1%) cases each. The approach for intravagal parathyroid adenomas has not been studied in itself due to the low volume of cases; however, there is literature describing approaches used for other intravagal pathology such as shwannoma and paraganglioma. The most common approach for intravagal tumors is transcervical either with or without parotidectomy or mandibulotomy.16,17 Other approaches include transoral, and more recently, transoral robotic surgery (TORS) has been explored in its utility to excise neurogenic neoplasms from the parapharyngeal space. In select cases, TORS may provide a solution to the instrumentation and visual limitations of the transoral approach to the parapharyngeal space.18 Due to the location of these tumors within or around the vagus nerve in relation to other vital structures, there are inherent risks to surgery. Postoperative morbidity in patients undergoing vagus nerve surgery includes recurrent laryngeal nerve palsy or Horner’s syndrome due to manipulation or sacrificing of the vagus. In addition to careful dissection and selecting the appropriate approach,
there may be a role for neural integrity monitor (NIM) electromyogram (EMG) tube placement in order to reduce postsurgical morbidity. Use of a NIM-EMG tube has been shown to aid in nerve preservation during the removal of vagal nerve schwannomas and decrease postoperative morbidity.19

4 | CONCLUSION

Intravagal parathyroid adenomas remain an exceedingly rare diagnosis; however, their true incidence may be higher than currently known. It is important to keep intravagal sites within the list of potential ectopic locations of parathyroid adenomas during the workup for primary or persistent hyperparathyroidism.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

MAL: involved in design and conception, data collection, data analysis, data interpretation, and manuscript drafting; BJB: involved in design and conception, data interpretation, and manuscript editing; PTD: involved in design and conception, data interpretation, manuscript editing, and supervision.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

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