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Case Report

Ectopic Parathyroid Adenoma in an 11-Year-Old Girl: Case Report and Literature Review

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ABSTRACT

Objective: Primary hyperparathyroidism secondary to an ectopic parathyroid adenoma is rare among children and adolescents.**Methods:** We describe the case of an 11-year-old girl with incidentally diagnosed primary hyperparathyroidism secondary to an intrathymic parathyroid adenoma and performed a review of the related literature.**Results:** ^{99m}Techneium sestamibi single-photon emission computerized tomography/computed tomography and 4-dimensional computed tomography confirmed the ectopic location of the adenoma. The patient underwent thoracoscopic thymectomy and remained normocalcemic with elevated parathyroid hormone showing a downward trend. Parathyroid hormone normalized 18 months after successful parathyroidectomy.**Conclusion:** We review the case of a rare mediastinal parathyroid adenoma in a pediatric patient and summarize the epidemiologic profile, diagnosis, and management of similar pediatric cases.© 2020 AACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Primary hyperparathyroidism secondary to an ectopic parathyroid adenoma is a rare entity, especially among the pediatric population.^{1,2} The only curative option is surgical removal.³ Accurate preoperative localization of parathyroid adenomas is essential to the success of minimally invasive parathyroidectomy. Ectopic adenomas may be located anywhere in the trajectory from the tongue to the mediastinum, usually in close association with the thymus.⁴ Identifying ectopic parathyroid adenomas can be challenging, and there is no consensus for the optimal imaging modality in this population. ^{99m}Techneium sestamibi scintigraphy (MIBI), neck ultrasound, computed tomography (CT), and magnetic resonance imaging

have been traditionally used to locate parathyroid adenomas.⁴ The use of combinations of imaging techniques, such as single-photon emission computerized tomography (SPECT)/CT and positron emission tomography/CT, have been increasingly reported in the literature, particularly when other modalities have initially failed to reveal the source of ectopic production of parathyroid hormone (PTH).^{5,6}

We present the case of an 11-year-old girl incidentally diagnosed with primary hyperparathyroidism who underwent the removal of an intrathymic parathyroid adenoma. Medical record review of this patient was approved by the New York Presbyterian Brooklyn Methodist institutional review board. We also performed a review of the literature of ectopic parathyroid adenomas among pediatric and adolescent patients aged up to 18 years old.

Case Report

An 11-year-old girl with no previous medical or surgical history presented to the emergency room with symptoms of sore throat, nasal congestion, and fever. She was not taking any medications or supplements. There was no family history of endocrinopathies. Her

Abbreviations: CT, computed tomography; MIBI, ^{99m}technetium sestamibi scintigraphy; PTH, parathyroid hormone; SPECT, single-photon emission computerized tomography.

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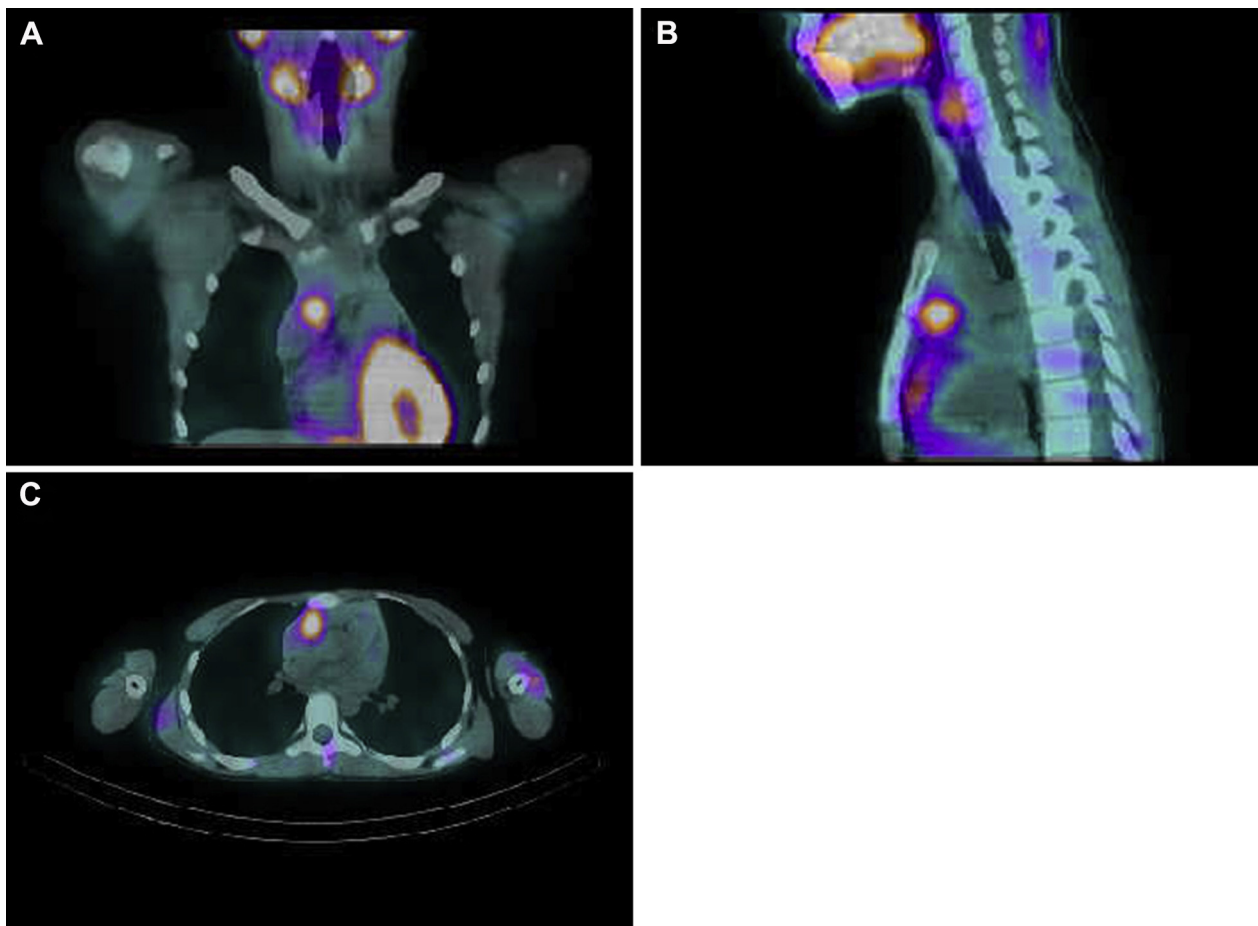


Fig. 1. Coronal (A), sagittal (B), and axial (C) views of ^{99m}Tc sestamibi with SPECT/CT demonstrating the ectopic parathyroid adenoma.

physical examination result was normal, except for right peritonsillar inflammation. She was admitted to the pediatric unit for intravenous antibiotics in the setting of peritonsillar cellulitis. During this time, a complete metabolic panel was drawn as part of the initial assessment of infection. The calcium level was 14.1 mg/dL (normal 8.5–10.1 mg/dL), and ionized calcium level was 1.90 mmol/L (normal 1.09–1.3 mmol/L). On further investigation, the PTH level was 230 pg/mL (normal 14–72 pg/mL), vitamin 25(OH)D level was 28.6 ng/mL (normal 30–100 ng/mL), phosphorus level was 1.8 mg/dL (normal 2.5–4.9 mg/dL), and alkaline phosphatase level was 181 U/L (normal 42–141 U/L). The patient underwent a neck CT without contrast as part of a peritonsillar abscess work up, which showed normal parathyroid anatomy.

On follow-up, she continued to be asymptomatic. The PTH level continued to rise to 839 pg/mL, and calcium level ranged between 12.2 and 14.1 mg/dL. Neck and upper chest MIBI showed a small focal area of moderately increased tracer uptake in the anterior mediastinal region slightly above the level of the heart, with suspicion for parathyroid adenoma. Genetic testing was negative for pathogenic variants or deletions/duplications in the *CASR*, *CDC73*, *CDKN1B*, *MEN1*, and *RET* genes (Hyperparathyroidism Panel, Invitae). No imaging studies to evaluate bone density were performed.

Because of suspicion of ectopic adenoma, MIBI SPECT/CT was performed, which showed abnormal focal uptake in the anterior mediastinum measuring $1.9 \times 1.0 \times 1.4$ cm, correlating

with an enhancing intrathymic nodule (Fig. 1). This finding was confirmed by 4-dimensional (4D) CT (Fig. 2). She underwent thoracoscopic thymectomy 5 months after her initial emergency room visit. The pathologic specimen revealed a $2.1 \times 1.6 \times 1.1$ cm well-circumscribed, unencapsulated nodule consistent with parathyroid adenoma inside an otherwise normal thymus. Intraoperative PTH level dropped to 99 pg/mL. On discharge, the calcium level was 9.3 mg/dL. She was discharged with a prescription of 1000 mg of elemental calcium twice daily for 16 days. Approximately 1 year after the surgery, she remained asymptomatic and was normocalcemic. The PTH level remained elevated but showed a downward trend under close monitoring with regular serum draws every few months in increasingly spaced intervals for 11 months (range 115.9–216 pg/mL). Eventually, the PTH level normalized 19 months after the operation. The vitamin 25(OH)D level ranged from 24.1 to 37.6 ng/mL in the same postoperative period.

Discussion

Our 11-year-old girl is one of the youngest cases of ectopic parathyroid adenoma in the limited pediatric literature. In this case, the initial MIBI located an abnormal uptake in the anterior mediastinum that was confirmed by MIBI SPECT/CT and 4D CT. Correlation with a second scan is sometimes necessary to verify the ectopic location of an adenoma, to map the relationships

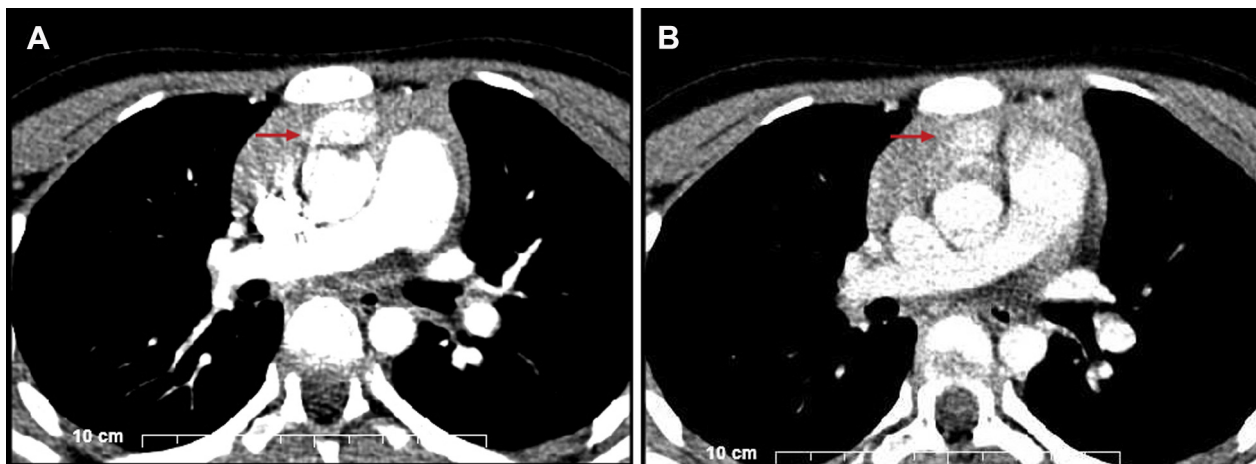


Fig. 2. Axial views of chest 4-dimensional CT demonstrating the ectopic parathyroid adenoma (arrow). A, Arterial phase. B, Delayed phase. CT = computed tomography.

with surrounding anatomic structures, and to guide the surgical localization, especially for minimally invasive procedures.⁷

Of note, the PTH level remained elevated for approximately 1 year after surgery before returning to normal levels. The patient remained asymptomatic and normocalcemic during this period. The PTH level was elevated postoperatively for years in a case of a 16-year-old patient with normocalcemia, reflecting the effect of hyperparathyroidism secondary to persistent vitamin D deficiency.⁸ In our case, vitamin 25(OH)D levels remained above 24 ng/mL during the follow-up period. This persistent elevation has been previously described in the literature among adult populations. In a review published in 2017, 33 studies reported data on this phenomenon, with a mean prevalence of 23.5% among postoperative cases.⁹ There is no reported association with primary hyperparathyroidism recurrence.⁹ Its etiology is not fully understood, and it is considered to be multifactorial. Vitamin D deficiency, a decrease in the glomerular filtration rate, the relative drop in postoperative calcium, the presence of hungry bone syndrome, and altered peripheral sensitivity to PTH have been proposed as possible mechanisms.⁹ In a recent study by Caldwell et al,¹⁰ approximately one third of the adult patients who underwent parathyroidectomy had persistent elevation of PTH level. Interestingly, this was associated with lower, but not abnormal, preoperative vitamin 25(OH)D levels compared with the group with normal postoperative PTH levels (26 ± 15 pg/mL vs 36 ± 11 pg/mL). There were no available postoperative vitamin 25(OH)D data reported. In our case, the vitamin 25(OH)D level was 29 ng/mL preoperatively, normalized without supplementation in the postoperative period, and subsequently dropped to 28 ng/mL 19 months after the surgery, when the PTH level normalized. Further studies evaluating the association of vitamin D insufficiency with this phenomenon are warranted.

Primary hyperparathyroidism in the pediatric population has been estimated to occur in 1 in 200 000 to 300 000 patients and is caused by a single adenoma in majority of cases.^{2,11,12} In a recent retrospective study of 86 pediatric patients by Rampp et al,¹¹ 22 cases of ectopic parathyroid adenomas were identified in 3 tertiary care facilities over the span of 20 years. In pediatric cohorts, the prevalence of ectopic adenomas among diagnoses of primary hyperparathyroidism ranges between 5% and 26%.^{2,11–14}

Our literature review for studies, including case reports, case series, and cohorts, of pediatric patients aged 18 years and below with ectopic parathyroid tumors yielded individual data for 33 cases (Table 1 and Supplementary Table). Two of the 33 cases were parathyroid carcinomas.^{17,22} There was no sex predominance. In approximately half of the cases, the localization of the adenoma was reported to be associated with the thymus, similar to ours. Our patient was asymptomatic at presentation and remained asymptomatic postoperatively. Among the 30 reports that included relevant medical history for the cases, a minority (5 of 30, 17%) of patients were diagnosed incidentally. Bone and renal involvement were the most commonly described end-organ pathologies. In only 1 of the cases, the patient was reported to have known multiple endocrine neoplasia 1 syndrome.⁷

The diagnostic challenge of ectopic parathyroid adenomas is highlighted by the fact that in 11 cases, the patient underwent more than 1 procedure until cure. Most patients underwent 2 or more different imaging modalities preoperatively, with half of the reports providing results on 3 or more imaging modalities (Table 1). The most commonly reported imaging modality was MIBI in 24 (including the current) of the cases, with a sensitivity of 71% (Table 2). Neck ultrasound results localized 2 intrathyroidal adenomas,^{29,41} an adenoma located in the suprasternal fossa,²¹ and an ectopic adenoma in a patient with multiple gland etiology (but not the ectopic adenoma of the same patient).¹² From studies in adult populations, the sensitivity of both ultrasound and MIBI regarding ectopic parathyroid adenomas is highly variable (US, 27%–89% and MIBI, 54%–100%).⁴ In the pediatric literature, Rampp et al¹¹ report a sensitivity of 10% for MIBI among ectopic cases. SPECT/CT identified the ectopic adenoma in 5 of 6 cases (including the current study) (Table 2). Notably, 4D CT has been increasingly used and is even used as a first-line imaging choice in some centers.⁴³ Its use in pediatric cases may be limited to a secondary role due to high radiation exposure.¹¹ To date, the pediatric literature on 4D CT has been limited to case reports, and future studies should investigate its role in diagnosing parathyroid adenomas in this population. Finally, the emerging ¹⁸F-fluorocholine positron emission tomography/CT, used in 1 of the cases, may play a role in complex cases when all other studies are negative.⁶

Table 1
Cases of Ectopic Parathyroid Adenoma and Carcinomas

Author	Year	Age	Sex	Presenting symptoms, medical history, end-organ damage signs	Imaging related to adenoma localization	Location of adenoma	Number of procedures
Schmidt et al ¹⁵	2001	8	M	Open tibial fracture secondary to trauma	US: neg, MRI: ND, MIBI: neg (Fpos)	Intrathymic	1
Çelik et al ¹⁶	2014	9	F	Mental retardation	US: neg, MIBI: neg	Close to common carotid artery	3
Righi et al ¹⁷	2008	10	M	Renal calcinosis	US: neg, MIBI: neg	Adjacent to thymus ^a	1
Wu et al ¹⁸	1985	10	M	URI, malaise, mandibular pain (dental abscess), polyuria	...	Intrathymic	1
Libánský et al ¹⁹	2008	10	F	Fatigue, decreased appetite and muscle strength Decreased bone density, subperiosteal brown tumor lesions, bilateral genu valgum deformities	US: Fpos, MIBI: neg, second MIBI: neg (Fpos), second US: neg, MRI: neg, CT: neg, PET/CT: neg, MIBI SPECT/CT: pos, second MRI: pos	Dorsolateral to left common carotid artery	2
Baird et al ²⁰	2011	10	...	Abdominal pain, acute pancreatitis	MIBI SPECT/CT: pos	Adjacent to thymus	1
Zhang et al ²¹	2010	10	F	Extremity pain, polydipsia, fatigue, anorexia emesis Osteoporosis	US: pos, MIBI: pos	Suprasternal fossa	1
Fiedler et al ²²	2009	10.5	M	Anorexia, fatigue, knee pain Thymus invasion	US: neg, MIBI: neg	Invading the thymus ^a	2
Yeşilkaya et al ²³	2009	12	F	Back and extremity pain, fatigue, anorexia, weight and height below the third centile Brown tumors in the posterior parietal and occipital bones	US: neg, MIBI: pos, MRI: pos	Intrathymic	1
Dhillon et al ²⁴	2013	12.5	M	Fatigue, muscle pains, h/o hand fracture	US: neg, MIBI: neg, second US: neg (Fpos), MRI: ND, 4D CT: pos	Within the carotid sheath	3
Bauman et al ⁵	2017	13	F	Anxiety, headaches, lethargy, muscle fatigue, impaired concentration	US: neg, MIBI SPECT/CT: neg, MRI: pos	Intrathymic	2
Morimoto et al ²⁵	2018	13	M	Abdominal pain Hydronephrosis, nephrocalcinosis	CT/3D CT: pos, MIBI: pos, SPECT: pos	Intrathymic	1
Kordahi et al ²⁶	2019	13	M	Fever, sore throat, difficulty swallowing, h/o chronic constipation, h/o painful gait	MIBI: neg, 4D MRI: pos, CT: pos	Left retropharyngeal space	1
Pitukcheewanont et al ⁸	2008	14	M	Abnormal gait, bilateral foot pain Flat feet, valgus deformities of knees, osteopenia, osteodystrophy (vitamin D deficiency rickets)	MIBI: pos, CT: pos	Intrathymic	1
Tonelli et al ⁷	2016	15	M	<i>MEN1</i> gene mutation, h/o pituitary microadenoma, h/o hyperprolactinemia	US: Fpos, MIBI: pos, MRI: pos, CT: pos	Near the tracheal bifurcation	1
Liu et al ²⁷	2019	15	M	Chronic fatigue & limb ostealgia, anorexia, weight loss Recurrent fractures, osteopenia	US: neg, MIBI: pos, 3D CT: pos	Intrathymic	1
Girard et al ²⁸	1982	15	M	Anemia, growth delay Osteopenia	...	Intrathymic	1
Lawson et al ²	1996	15	M	Renal colic Osteopenia, nephrolithiasis	US: neg (Fpos), second US: neg, Tc: ND, CT: neg, MRI: neg, venography: pos	Mediastinum	2
Bender et al ²⁹	1992	16	F	Nephrolithiasis	US: pos, CT: neg, MRI: pos, thallium/Tc: pos	Intrathyroidal	2
Birdas et al ³⁰	2005	16	M	...	MIBI: pos	Anterior to the junction of R atrium & superior vena cava	1
Li et al ¹²	2012	<16	...	Urolithiasis, bone involvement	US: neg, MRI: neg, MIBI: pos	Intrathymic ^b	1
Heller et al ³¹	1994	17	F	Nephrolithiasis	At least 2 pos imaging results	Mediastinum	2
Minamiya et al ³²	2009	17	F	Urolithiasis	CT: pos, MIBI: pos	Intrathymic	1
Daruwalla et al ³³	2015	17	F	Nephrolithiasis, fatigue, flat affect	US: neg, MIBI (reviewed by surgeon): pos	Intravagal	1
Dhiwakar et al ³⁴	2016	17	F	Bony growths in mandible & hard palate Giant cell reparative granuloma of mandible, lytic bone areas	MRI: pos, SPECT/CT: pos, MIBI: pos	Intrathyroidal	1
Boccalatte et al ³⁵	2018	18	M	Hypertension, asymptomatic	US: neg, MIBI SPECT: neg, MRI: neg, ¹⁸ F-choline PET/CT: pos	Intrathymic	1
Wells et al ³⁶	1991	18	F	Nephrolithiasis	CT: neg, MRI: neg, thallium/Tc: neg	Intrathymic	2
Martinez et al ³⁷	1995	18	F	...	US: neg, thallium/Tc neg, CT: neg, MRI: neg, MIBI: pos	Under the arch of the ascending aorta	2
Deeb et al ³⁸	2001	18	F	...	MRI: pos, MIBI: pos	Intrathymic	2

Table 1 (continued)

Author	Year	Age	Sex	Presenting symptoms, medical history, end-organ damage signs	Imaging related to adenoma localization	Location of adenoma	Number of procedures
Spinelli et al ³⁹	2012	18	F	Asymptomatic	US: neg, thallium: neg, MIBI: pos, SPECT: pos, CT: pos, live labeling of erythrocytes, Tc-pyroscent:- SPECT: pos, MRI: neg	Intrathyroidal	1
Saad et al ⁴⁰	2014	18	F	Chronic weakness, fatigue, polyuria, vomiting, pregnancy at 23 weeks of gestation Nephrolithiasis, recurrent pyelonephritis	Half-dose MIBI: pos	Superior posterior mediastinum	1
Wang et al ⁴¹	2014	18	M	Pain in right shoulder Pathologic fracture & brown tumor of right upper humeral shaft	US: pos, CT: pos, MIBI: pos	Intrathyroidal	1
Ruanpeng et al ⁴²	2017	18	F	Fatigue, depression Recurrent nephrolithiasis	MIBI SPECT/CT: pos, CT: pos	Intrathyroidal	1

Abbreviations: CT = computed tomography; F = female; Fpos = false-positive; h/o = history of; M = male; MIBI = ^{99m}technetium sestamibi; MRI = magnetic resonance imaging; ND = nondiagnostic (technically suboptimal or nonspecific findings); neg = negative; PET = positron emission tomography; pos = positive; R = right; SPECT = single-photon emission computerized tomography; Tc = technetium; URI = upper respiratory infection; US = ultrasound of neck.

^a Carcinoma.

^b The patient had a second entopic parathyroid adenoma; ultrasound and MRI were positive for the presence of the entopic adenoma but negative for the presence of the ectopic adenoma.

Table 2
Imaging Data From 31 Cases of Ectopic Parathyroid Tumors

Author	Year	US	MIBI ^a	CT	4D CT	MRI ^b	SPECT/CT	PET/CT
Wells et al ³⁶	1991	X	...	X
Bender et al ²⁹	1992	✓	...	X	...	✓
Martinez et al ³⁷	1995	X	✓	X	...	X
Lawson et al ²	1996	X/X	...	X	...	X
Schmidt et al ¹⁵	2001	X	X	X
Deeb et al ³⁸	2001	...	✓	✓
Birdas et al ³⁰	2005	...	✓
Righi et al ¹⁷	2008	X	X
Libánský et al ¹⁹	2008	X/X	X/X	X	...	X/✓	✓	X
Pitukcheewanont et al ⁸	2008	...	✓	✓
Fiedler et al ²²	2009	X	X
Yeşilkaya et al ²³	2009	X	✓	✓
Minamiya et al ³²	2009	...	✓	✓
Zhang et al ²¹	2010	✓	✓
Baird et al ²⁰	2011	✓	...
Spinelli et al ³⁹	2012	X	✓	✓	...	X
Li et al ¹²	2012	X	✓	X
Dhillon et al ²⁴	2013	X/X	X	...	✓	X
Çelik et al ¹⁶	2014	X	X
Saad et al ⁴⁰	2014	...	✓
Wang et al ⁴¹	2014	✓	✓	✓	...	✓
Tonelli et al ⁷	2016	X	✓	✓	...	✓
Daruwalla et al ³³	2015	X	✓
Dhiwakar et al ³⁴	2016	...	✓	✓	✓	...
Bauman et al ⁵	2017	X	✓	X	...
Morimoto et al ²⁵	2018	...	✓	✓
Ruanpeng et al ⁴²	2017	✓	✓	...
Boccalatte et al ³⁵	2018	X	X	...	✓
Kordahi et al ²⁶	2019	...	X	✓
Liu et al ²⁷	2019	X	✓	✓
Flokas et al (current case)	✓	X	✓	...	✓	...

Abbreviations: CT = computed tomography; MIBI = ^{99m}technetium sestamibi scintigraphy; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission computerized tomography.

X: negative, false-positive, and nondiagnostic results; ✓: true positive results.

^a SPECT not depicted.

^b 4D MRI not depicted. The patient had a second entopic parathyroid adenoma; ultrasound and MRI were positive for the presence of the entopic adenoma but negative for the presence of the ectopic adenoma.

Conclusion

In conclusion, we report the case of a mediastinal parathyroid adenoma in a pediatric patient and highlight appropriate methods of diagnosis, cure, and follow-up of this rare disease, supplementing with a review of reported pediatric and adolescent

cases. In our case, monitoring of the PTH level for 18 months postoperatively showed persistent elevation of the PTH level without any signs of recurrence of hyperparathyroidism or concurrent vitamin D deficiency. This phenomenon, described in adult cases, has not been adequately studied in the pediatric population.

Disclosure

The authors have no multiplicity of interest to disclose.

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