Primary hyperparathyroidism: fifth parathyroid intrathymic adenoma in a young patient

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Abstract

The clinical case described in this paper deals with a young female patient affected by primary hyperparathyroidism caused by an ectopic parathyroid adenoma of a supernumerary intrathymic parathyroid. The patient had hypercalcemia, in association with increased levels of parathormone, but was otherwise asymptomatic. Genetics tests for mutation of the MEN1, HRPT2, and CaSR genes were negative. She therefore underwent laboratory and instrumental tests but localization results in the neck were negative – only an intrathymic nodule was visualized. The complete surgical ablation of the thymus was conducted, which highlighted a nodule that, at histological examination, was shown to be an adenoma of a fifth parathyroid gland. The existence of a fifth, hyperfunctioning, intrathoracic parathyroid appears to be a rare cause of primary juvenile sporadic hyperparathyroidism. This peculiar clinical case could be of interest in similar cases evaluated by other surgeons.

Keywords: adenoma; ectopic parathyroid; hypercalcemia; pediatric; primary hyperparathyroidism.

Introduction

Primary hyperparathyroidism (PHP) is the most common cause of hypercalcemia in the ambulatory population (1). Usually, PHP is due to a single adenoma in a typical site or, more rarely, in an ectopic site (80%–85%); only occasionally is PHP due to multiple glandular hyperplasia (12%–15%), double adenoma (2%–3%), or parathyroid carcinoma (2). An unusual anatomical location of a parathyroid adenoma makes the diagnosis and the therapy problematic. This paper describes the clinical case of a young female patient, completely asymptomatic, having a PHP caused by an adenoma of a fifth intrathymic ectopic parathyroid. In the literature, the occurrence of PHP due to a parathyroid adenoma on a supernumerary ectopic parathyroid is rare (0.7%) and the ectopic gland is usually located in the caudal portion of the neck or in the mediastinum or, very rarely, inside the thymus (3).

After Institutional Review Board approval, written informed consent was obtained from the parents for publication of this case report and accompanying images.

Clinical case

A completely asymptomatic 18-year-old female patient underwent routine hematoclinical tests, which showed high serum calcium (12.9 mg/dL). Laboratory and instrumental diagnostic tests to find the cause of the hypercalcemia were carried out. The pathological anamnesis did not detect any relevant data. Family history was negative for hereditary hypercalcemic disorders. Neck palpation revealed neither a significant nodular lesion in the central region nor laterocervical or supravclavicular lymphadenomegaly. Repeated hematological tests confirmed an increase in the serum calcium levels (from 13.3 mg/dL to 15.9 mg/dL; normal range: 8.40–10.20), and in the parathormone (PTH) concentration (279.0 pg/mL; normal range: 8.0–65.0).

An ultrasound scan of the neck did not detect significant changes in the thyroid or the adjoining structures. Scintigraphy after intravenous administration of 74 Mbq thallium 201 (201Tl: IBA Molecolar Chemin du Cyclotron 3, 1348 Louvain-La-Neuve, Belgium) did not reveal areas of hyperfixation that could be related to hyperfunctioning parathyroid tissue. Further scintigraphy, performed 15 min after the intravenous administration of 740 MBq technetium (99mTc-Sestamibi: Cardiolite® Bristol-Myers Squibb Medical Imaging, North Billerica, MA, USA) highlighted a zone of hyperaccumulation in the front mediastinal site (Figure 1). Single-photon emission computed tomography (SPECT) scans of the cervicothoracic region confirmed
the presence of a clear hyperaccumulation zone in the front mediastinal site. With visualization of the great thoracic vessels through live labeling of the erythrocytes (555 MBq $^{99m}$Tc-Pyroscint: DuPont Pharma S.A., Brussels, Belgium) and with further SPECT a lesion in front of the aortic arch became evident (Figure 2). This indicated the presence of hyperfunctioning ectopic parathyroid parenchyma in the front mediastinal site. Computed tomography (CT) of the thorax and mediastinum (performed in basal conditions and 1 h after the administration of contrast medium with a thin-layer scan) highlighted a modest quantity of retrosternal thymic tissue. On the side of the residue, in the left paramedian site, a small nodule with an average diameter of 5.0 mm was evidenced and was interpreted as an ectopic parathyroid adenoma. Magnetic resonance imaging (MRI) of the neck then confirmed the tomographic and ultrasonographic picture of the absence of significant alterations at the thyroid level and at the anatomical sites that correspond to the parathyroid glands. MRI of the thorax highlighted the presence of a small thymic residue in its anatomical site by the anterosuperior mediastinum, with no certain ectopic parathyroid tissue. Analysis for the MEN1, CaSR, and HRPT2 genes revealed a lack of mutations in their coding regions.

On the basis of the instrumental and laboratory investigations and the clinical picture, and with a diagnosis of a suspect parathyroid adenoma in an ectopic site, surgical exploration by transversal cervicotomy was necessary. During the operation, the thyroid compartments were carefully explored and four morphologically normal parathyroid glands were identified. By contrast, the right superior parathyroid appeared globose, was larger than the others and its density was higher. A biopsy was carried out and an extemporary histological test highlighted only parathyroid hyperplasia. A median partial sternotomy was then performed. At the opening of the thorax the thymus was totally excised and its left side found to contain a nodule with an average diameter of 10 mm. An extemporary histological test of the nodule detected pathological parathyroid tissue. The intraoperative serum PTH level was measured immediately after removal of the thymus and was markedly reduced ($\Delta$PTH 125.0 pg/mL). The final histological test confirmed the diagnosis of a parathyroid adenoma of an ectopic supranumerary gland. The postoperative course was regular and, at the time of discharge, serum calcium levels (9.1 mg/dL) and PTH values ($<$1.0 pg/mL) were normal. After 2 years of follow-up, the patient is asymptomatic and regular hematological tests are normal.

**Discussion**

The peculiarity of this case report is due to the rarity of an ectopic supernumerary parathyroid gland located intrathyroidally in sporadic juvenile PHP. Ectopic parathyroid adenomas are responsible for 15% of cases of PHP. The superior parathyroid glands arise from the fourth branchial complex, along with the thyroid gland. Minimal descent and the close relationship to the thyroid make ectopic superior glands relatively uncommon (about 2%). Ectopic inferior parathyroid glands are more common. Since the thymus and the inferior parathyroid glands both arise from the third branchial complex and descend together, ectopic inferior glands can be found in the anterior mediastinum. It is also possible, although rare, to find an inferior parathyroid adenoma high in the neck resulting from early developmental arrest (4).

This case emphasizes that instrumental tests, such as echography or scintigraphy with $^{99m}$Tc-sestamibi, in association with CT with or without contrast medium and with MRI, might not be enough to enable preoperative localization of an intrathoracic ectopic parathyroid adenoma (5, 6). The accumulation
and retention of $^{99m}$Tc-sestamibi at the parathyroid level is due to the tissue’s metabolic activity and is essentially influenced by the hematic flux, the dimensions of the gland(s), and by the metabolic activity of the mitochondria. Like other radiomimetic agents used for scintigraphic imaging (e.g., $^{201}$Tl), $^{99m}$Tc-sestamibi concentrates both in the thyroid and the parathyroid tissue within a few minutes after intravenous administration. However, this tracer is particularly useful for imaging the parathyroid glands because there is a variation in washout rate between the two tissues (washout tends to be more rapid in the thyroid than the parathyroids). The different kinetics probably depend on the down-regulation of the P-glycoprotein system, which acts as the efflux transporter for $^{99m}$Tc-sestamibi in the parathyroid tissue. Scintigraphy with $^{99m}$Tc-sestamibi can accurately locate parathyroid adenomas in 85%–95% of the patients affected by PHP (7, 8). The use of SPECT considerably improves the localization of particular ectopic sites that are otherwise difficult to explore, such as the retroesophageal space and the mediastinal region. After the recent introduction of hybrid detection systems such as SPECT-CT, the localization of ectopic lesions has become more precise (9–11). The role of preoperative evaluation for location of an ectopic parathyroid is still controversial, as the presence of abnormal parathyroids can be identified during the initial surgical exploration by an experienced surgeon in 90%–95% of cases. Moreover, in PHP, bilateral exploration of the neck to identify all the parathyroids must be performed in all cases, irrespective of the location suspected as a result of preoperative research. An accurate investigation must be conducted in more frequent ectopic sites (10, 12). A stomatotomic approach is necessary, as in our clinical case, even in the case of a suspected mediastinal adenoma. An ectopic superior parathyroid is usually in a retroesophageal site, while an inferior supernumerary parathyroid is more frequently in the anterosuperior or intrathyimic mediastinum. The best surgical approach for mediastinal ectopic parathyroids is widely debated in the literature (9, 10, 13). Sometimes a collar stomatomy might be sufficient for their removal, whereas a transthoracic approach is necessary in those rare cases of adenoma that are located more caudally or in an unfavorable retrosternal position (14). The open approach prescribes a sternotomy or a thoracotomy. A thoracoscopic approach has been used for the first time by Profranter and his staff (15), whereas a video-assisted mediastinoscopic or thoracoscopic (VAM) approach to ectopic parathyroid adenoma is reported in several articles (16). Radio-controlled surgery is of great help in PHP. It can be performed only when preoperative scintigraphy identifies a hyperaccumulation of the radiomimetic agent in a single parathyroid adenoma. The gamma probe allows immediate ex vivo confirmation of the ablation of a parathyroid gland in the case of mediastinal damage, and a different diagnosis for other removed tissues, such as lymph nodes, thymus, and adipose tissue, which typically do not capture the radiomimetic agent. In our case, we preferred to proceed in an open way through a partial median sternotomy, on the basis of a difficult preoperative diagnosis and the suspected unfavorable retrosternal position of the parathyroid adenoma. In conclusion, the ectopic localization of a parathyroid adenoma is a difficult condition to recognize and even more when sporadic PHP is diagnosed in young patients. The possibility of an intrathyimic location should be kept in mind even in non-hereditary syndromes, as in our case.

Figure 2  Single-photon emission computed tomography (transverse sections) with double tracer 20 min after intravenous administration of 740 MBq $^{99m}$Tc-Pyroscint for the live labeling of erythrocytes: a zone of hyperaccumulation of the radiomimetic agent is evident at the front of the aortic arch. Such a reaction is related to the presence of ectopic hyperfunctioning parathyroid parenchyma in the anterior mediastinal site. No pathological findings were evident at the cervical site.
References