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Multicenter Study of 19 Aortopulmonary Window Parathyroid Tumors: The Challenge of Embryologic Origin

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Abstract
Background Ectopic abnormal parathyroid glands are relatively common in the superior mediastinum but are rarely situated in the aortopulmonary window (APW). The embryological origin of these abnormal parathyroid glands is controversial. The purpose of this investigation was to investigate the embryological origin and the surgical management of abnormal parathyroid glands situated in the APW.
Methods The databases of patients operated on for primary, secondary, and tertiary hyperparathyroidism at eight European medical centers with a special interest in endocrine surgery were reviewed to identify those with APW adenomas. Demographic features, localization procedures, and perioperative and pathology findings were documented. The embryological origin was determined based on the number and position of identified parathyroid glands.
Results Nineteen (0.24%) APW parathyroid tumors were identified in 7,869 patients who underwent an operation for hyperparathyroidism (HPT) and 181 patients (2.3%) with mediastinal abnormal parathyroid glands. Ten patients had primary, eight had secondary, and one had tertiary HPT. Sixteen patients had undergone previous unsuccessful cervical exploration. In three patients, an APW adenoma was suspected by preoperative localization studies and was cured at the initial operation. Sixteen patients had persistent HPT of whom 15 were reoperated, resulting in 6 failures. Evaluation of 17 patients who had bilateral neck exploration allowed us to determine the most probable origin of the APW parathyroid tumors: 12 were supernumerary, 4 appeared to originate from a superior, and 1 from an inferior gland.
Conclusions Abnormal parathyroid glands situated in the APW are rare and usually identified after an unsuccessful cervical exploration. Preoperative imaging of the mediastinum and neck are essential. The origin of these ectopically situated tumors is probably, as suggested by our data, from a supernumerary fifth parathyroid gland or from abnormal migration of a superior parathyroid gland during the embryologic development.

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Introduction

Localization and resection of ectopic parathyroid tumors (hyperplastic or adenomatous) is a major challenge in parathyroid surgery. Ectopic parathyroid tumors occur in

approximately 20% of patients and are a major cause for an unsuccessful neck exploration by an experienced surgeon [1–3]. Ectopic parathyroid tumors also may be a supernumerary or fifth parathyroid gland in 2.5–22% of patients [4–6]. Supernumerary glands are usually located within the thymus or perithymic fat, in the upper anterior mediastinum [1, 7, 8].

Historically approximately 2% of mediastinal parathyroid adenomas require a median sternotomy for removal [9, 10]. The increasing use of accurate preoperative imaging procedures (sestamibi scan, magnetic resonance imaging (MRI), CT scan) has substantially altered the surgical strategy for the management of mediastinal parathyroid lesions, because many of these tumors are suspected preoperatively [11]. Currently more selective approaches, such as anterior mediastinoscopy or thoracoscopy, have proved successful and are less aggressive than traditional thoracic approaches [12–16]. Most mediastinal anterior or posterior parathyroid tumors situated cephalad to the innominate vein can be removed via a cervical incision. This is not true for tumors in the APW.

The APW is the region of the middle mediastinum located under the concavity of the aortic arch, between the aorta and the left pulmonary artery. The ascending and descending aortic segments are considered its antero- and postero-lateral limits. The embryologic reason why some parathyroid tumors are situated in the APW is unknown and current hypotheses include abnormal migration of an upper or lower parathyroid gland during embryologic development or supernumerary gland with four other parathyroid usually at normal location.

The purpose of this multicenter, retrospective study was to determine the frequency of APW parathyroid tumors, the embryologic reasons for their ectopic position, and the results of localization procedures and surgical treatment.

Materials and methods

Between 1958 and 2004, 7,869 patients underwent operations for primary, secondary, and tertiary hyperparathyroidism at eight University Medical Centers with a special interest in endocrine surgery in France, Belgium, and Spain (Poitiers, Lille, Marseille, Lyon, Limoges, Angers, France; Liege, Barcelona). A mediastinal adenoma was diagnosed in 181 cases (2.3%), of which 19 adenomas were located in the APW (0.24%). A retrospective chart review of these 19 cases was performed, and the following variables were documented: age, sex, laboratory data (s-Ca and PTH), localization techniques (ultrasonography, sestamibi scintigraphy, computed tomography scan with IV contrast, MRI, and others), surgical strategy, number and localization of identified normal or enlarged abnormal parathyroid glands, pathology reports, and postoperative complications. When initial parathyroid operations were unsuccessful, these same data were analyzed for the reoperation.

According to the number and position of parathyroid glands identified in patients with previous bilateral neck exploration, the most plausible hypothesis for the embryologic origin of an APW adenoma was formulated.

Results

Eight men and 11 women with a mean age of 47 (range, 15–87) years were included in the study. Most patients presented with a combination of symptoms typical of hyperparathyroidism, such as fatigue (8 patients), bone disease or pain (13 patients), and renal involvement (10 patients). Ten patients had primary, eight had patients secondary, and one patient had tertiary hyperparathyroidism. Mean preoperative s-Ca and PTH levels were 3.17 (range, 2.5–5.25) mmol/l and 755 (range, 87–575) pg/ml, respectively.

Localizing tests before the initial operation

All patients had neck ultrasound examination before their mediastinal exploration and all, as expected, were negative. Six patients had a chest CT, which identified a suspected mediastinal parathyroid tumor in three cases. Nine patients had Tc-sestamibi or thallium scintigraphy, and three probable adenomas were identified in the APW. One patient had an MRI and another had highly selective venous catheterisation for parathyroid tumors; neither test was diagnostic. Initial surgery was performed via cervical approach (15 cases) or via cervico-sternotomy (4 cases). A thymectomy was performed in 13 cases. In three cases the abnormal parathyroid gland was situated in the APW, was found, and patients were cured. In 16 cases, "adenomas" or "hyperplastic" parathyroid glands were resected (mostly in patients with renal hyperparathyroidism), but patients were not cured.

Localizing tests before reoperation

To localize the missing parathyroid tumor in the 16 patients with persistent hyperparathyroidism, new localizing studies were performed in 15 cases (one patient operated in 1964 was not reexplored because of old age). The results of these studies are presented in Table 1. In all 15 patients, an abnormal parathyroid gland was identified in the APW. In six patients, only one preoperative localization study was positive; two localization studies were positive in nine patients and three in three patients. The radiological appearance in the chest CT scan of two APW adenomas is shown in Figs. 1 and 2.

Table 1 Results of localizing studies in 15 patients with persistent hyperparathyroidism before reoperation

Test	Positive	Negative
Ultrasonography	1 (false-positive)	14
Thallium scintigraphy	5	1
Tc-sestamibi scintigraphy	5	4
CT scan	6	4
MRI	3	2
Arteriography	1	0
Venous sampling	1	0
Casanova's test	1	0

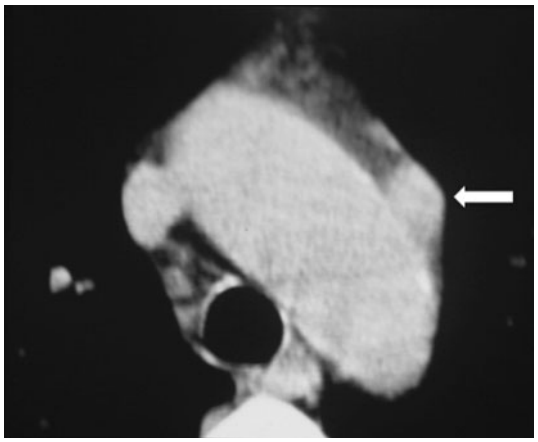

Fig. 1 A hyperplastic fifth gland in the upper part of the aortopulmonary window as seen on a CT scan in a patient with renal hyperparathyroidism (observation from ASS)

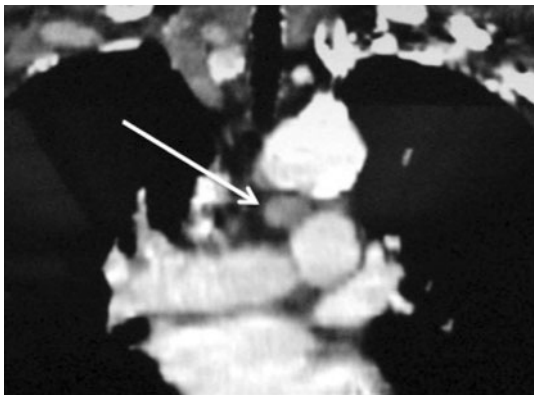

Fig. 2 A hyperplastic fifth gland in the aortopulmonary window as seen on a frontal CT scan in a patient with renal hyperparathyroidism (observation from ASS)

Surgical strategy

Fifteen patients were reoperated. Time between initial operation and reintervention ranged from 1 to 20 years. Median sternotomy was performed in four patients,

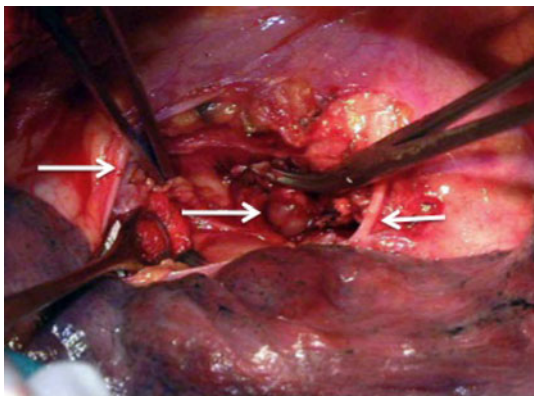

Fig. 3 Left thoracotomy through the fourth intercostal space to remove an adenoma situated deep in the aortopulmonary window. The *ligamentum arteriosum* has been divided. (Left arrow) phrenic nerve; (middle arrow) enlarged parathyroid gland; (right arrow) vagus nerve. Same patient as Fig. 2

cervico-sternotomy in six patients, repeated neck exploration in three patients, a left thoracotomy in one patient (Fig. 3), and an anterior thoracotomy in one patient. APW adenomas were found in nine patients. In three patients intrathymic or superior mediastinal adenomas also were found. In three patients no abnormal parathyroid glands were identified. In all, 6 of the 15 patients had persistent hyperparathyroidism despite reoperation. Further localizing studies in these six patients suggested a lesion in the APW in all patients either by Tc-sestamibi scintigraphy [4], CT scan [4], and/or MRI [3]. These six patients underwent a third surgical procedure: one thoracotomy, two thoracoscopies, one median sternotomy, and two cervico-sternotomies. A parathyroid tumor was found in the patients in the APW. In one patient, the adenoma could not be removed via a median sternotomy, and therefore, the patient underwent a successful left thoracotomy at same time.

Pathology and origin of the APW adenomas

Eventually, 18 of 19 patients were cured of their disease. In 12 patients the parathyroid lesion was an adenoma, and in 6 patients it was a hyperplasic parathyroid gland. Thymic tissue was not found near the parathyroid tumor in the APW.

Detailed analysis of the operative and pathology reports allowed us to speculate about the origin of APW tumors. In 12 patients, 4 parathyroid glands were identified in the neck; thus, in these patients the APW adenoma corresponded to an enlarged supernumerary gland. A supernumerary gland was found in 88% of patients with renal hyperparathyroidism and in 50% of patients with primary hyperparathyroidism. In five patients, a parathyroid gland was missing at cervical exploration: in four patients it was

a superior and in one patient an inferior gland. In these patients, the APW could have originated in a supernumerary gland or in a gland that was missed during initial exploration due to abnormal migration during embryologic development. In the remaining two patients, it was not possible to determine the origin of the adenoma because the neck was not explored (only mediastinal approach).

Discussion

The first patient with primary HPT and mediastinal parathyroid adenoma was reported in 1932 by Dr. Edward Churchill. His patient, Captain Charles Martell, unfortunately had six unsuccessful neck explorations before his mediastinal tumor was removed [17]. To our knowledge, the first parathyroid adenoma in the APW was reported by Cohn and Silen in 1982 [18].

According to traditional anatomical descriptions, the superior parathyroid glands are located on the posteromedial aspect of the thyroid near the tracheoesophageal groove and just cephalad to the intersection between the recurrent laryngeal nerve and the inferior thyroid artery. Approximately 90% of upper parathyroid glands are situated at this site. Ectopic locations closely connected to their embryologic course of migration have been extensively described in the literature. Akerström et al. reported that 1% of superior parathyroid glands are located in the retropharyngeal or retroesophagal space [1]. Most of these parathyroid tumors can be removed via a cervical incision. In the 1991 report by the French Association of Surgery, 4.8% of superior parathyroid glands were found to have migrated down to the posterosuperior mediastinum [19]. The blood supply to these glands comes from the inferior and superior thyroid arteries, and their removal can almost always be performed via a cervical approach. Other, more uncommon, ectopic location of the superior glands are high retropharyngeal, intrathyroidal, or within the carotid sheath [1, 2].

The inferior parathyroid glands are more widely distributed and often migrate embryologically within or near the thymus. The most common location for the inferior parathyroid gland is along the lateral side of the inferior thyroid pole, on the thyroid lobe, anterior to the recurrent laryngeal nerve, in the thyrothymic ligament or within the thymus [1]. Truly intrathyroidal parathyroid glands account for less than 3% of patients [7]. In approximately 1% of patients, the inferior gland is undescended and found high above the thyroid lobe at the level of the carotid sheath or submandibular gland, but Akerström et al. [1] believe that this site may occur more frequently.

The knowledge of parathyroid gland embryology allows a proper understanding of the normal and ectopic location of the parathyroid glands and helps with the intraoperative decision-making process. The thyroid, parathyroid glands, and thymus originate from the pharyngeal region. In 1937, Norris studied the morphogenesis of the parathyroid glands and described five stages in the developmental process [20]. The preprimordial stage (embryo 4–8 mm in length) is characterized by the formation of the pharynx and development of the third and fourth pouches. During the early primordial stage, differentiation of large and clear cells occurs in the third and fourth pouches. At the third stage (embryo 10–18 mm in length)—the branchial complex stage—the third and fourth pouches separate from each other. The third branchial pouch gives rise to the thymus and the inferior parathyroid glands (PIII), and the fourth branchial complex to the lateral thyroid and the superior parathyroid glands (PIV). The thymus and PIII develop near each other early in this third stage. The thymus migrates caudally until it reaches the pericardium, whereas PIII usually remains at the upper end of the thymus in the thyrothymic ligament or adjacent to it in the perithymic fat. The fourth stage is characterized by separation of the third and fourth branchial pouches. Separation of PIII from the thymus usually occurs when PIII reaches the lower thyroid pole. There is no further migration of the fourth branchial complex. Separation of PIV from the lateral thyroid occurs when the medial and lateral thyroid anlages merge. In the last stage, the parathyroid glands reach their final position.

It is well documented that anterior mediastinal parathyroid tumors develop from inferior glands and, as mentioned, often are embedded within the thymus [21, 22]. A transcervical thymectomy allows the resection of most of these adenomas. This is especially true in young patients whose thymus is well developed. It also is well recognized that PIV ectopias are most often found in the posterior upper mediastinum in the tracheoesophageal groove. However, what is the embryologic origin of ectopic APW parathyroid lesions?

In 1996, Doppman et al. [23] reported 10 cases of APW adenomas operated on in three centers, and reviewed 15 more cases from the literature [9, 18, 23–32]. As in the present study, most of the patients had had a previous unsuccessful cervical exploration. In almost 60% of the cases, four parathyroid glands had been identified in the neck and it was possible to conclude that the parathyroid tumors situated in the APW were located in a supernumerary gland. In our series, at least 58% of the APW parathyroid tumors also were supernumerary glands.

Supernumerary glands can be found in 2.5–22% of people [1]. In secondary hyperparathyroidism, the frequency is even higher (5–37% of patients) [4, 5]. They are usually discovered only when enlarged and in the setting of persistent hyperparathyroidism [5, 6, 33]. Mediastinal

parathyroid tumors are usually found in the thyrothymic ligament, in the thymus, or in perithymic fat [4, 34]. These locations correspond to the PIII migration area [4]. During embrionary development, fragments of parathyroid tissue sometimes separate. In the presence of a proliferative stimulus, such as MEN 1 or chronic renal failure, these parathyroid fragments enlarge and become supernumerary enlarged glands [34]. When supernumerary glands are identified in the middle mediastinum or near pericardium, an early separation of PIV may be invoked [29]. Proye et al. [29] have proposed three hypotheses to explain the origin of APW adenomas [29]:

1) When PIII individualizes from the third branchial pouch, it is theoretically possible that some parathyroid cell remain attached to the pericardial anlage. In this case, some thymic tissue should be found near the adenoma;
2) Based on the observations of Gilmour [35], who noted that PIV is in contact with pericardium in the 3-mm embryo, and those of Frazer [36], who reported that the fourth branchial pouch surrounds the aortic arch on the left side, some parathyroid cells could separate from the main gland and remain attached to the pericardium (Fig. 4).

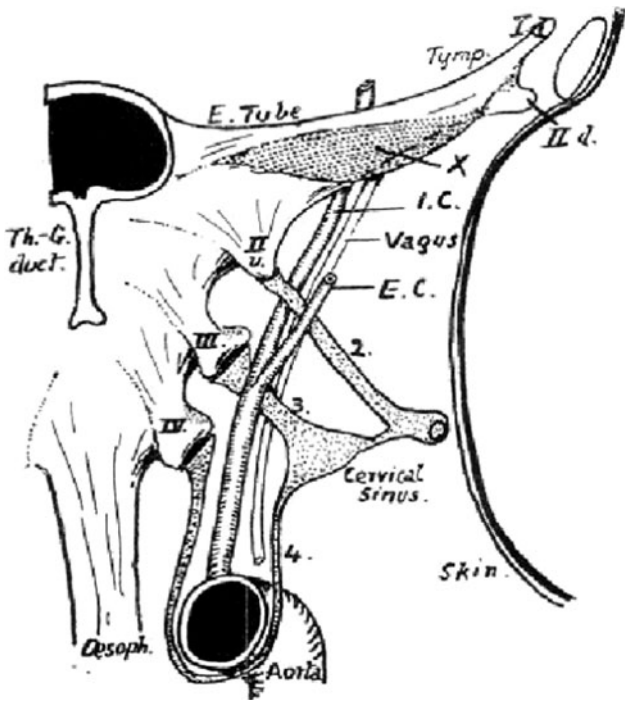

Fig. 4 Schematic figure to show the vestigial structures in the neck, with their relations to main arteries and nerves (Frazer, 36). *Id, IId*, dorsal angles of first and second lateral pouches. *IIv, III, IV,* internal pharyngeal ducts derived from ventral angles of second, third, and fourth lateral pouches. *2, 3, 4,* external pharyngeal ducts derived from second, third, and fourth external grooves. *X*, layer of entodermal cells cut off from lower part of eustachian tube

3) In the 7.5- to 11-mm embryo, PIV develops close to the sixth branchial artery. If separation of PIV occurs at this stage, some parathyroid tissue would be present near the origin of the future right pulmonary artery.

Two findings favor the two last hypotheses. First, APW adenomas often are found just above or behind the right pulmonary artery [9, 23, 26, 37–39], and it often is necessary to open the pericardium or to divide the *ligamentum arteriosum* to excise an APW adenoma. Second, thymic tissue has never been found near the abnormal parathyroid tissue in the APW, although it could be present but not removed [22, 23, 29].

The origin of blood supply to APW adenomas may help to elucidate the origin of APW adenomas. Five of nine patients with APW adenomas, reported by Doppman et al. [23], had positive preoperative arteriograms. In all cases the blood supply originated from bronchial arteries and never from vessels supplying the thymus. In our only patient who underwent arteriogram, the arterial blood supply originated from the internal mammary artery.

The best surgical approach to remove a parathyroid tumor from the APW remains controversial. Although most of them have been approached through a transternal route, their position in the middle mediastinum—often below the aortic arch—makes a left approach more suitable. A thoracoscopic left-lateral approach allows an excellent visualization of the phrenic and vagus nerve, which represent the natural anterior and posterior limits of the space in which the mediastinal pleura is opened. In addition, it offers a better view of the *ligamentum arteriosum*, which has to be divided often to expose a deep seated parathyroid tumor sitting on the pulmonary artery.

In conclusion, the absence of thymic tissue adjacent to the APW parathyroid gland and the mediastinal arterial supply to parathyroid tumors in the APW suggest that either there is in situ development of a supernumerary gland or an aberrantly situated superior parathyroid gland.

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