Supernumerary parathyroid glands in hyperparathyroidism associated with multiple endocrine neoplasia type 1

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Summary

Objective: To evaluate frequency, anatomic presentation, and quantities of supernumerary parathyroids glands in patients with primary hyperparathyroidism (HPT1) associated with multiple endocrine neoplasia type 1 (MEN1), as well as the importance of thymectomy, and the benefits of localizing examinations for those glands. **Methods:** Forty-one patients with hyperparathyroidism associated with MEN1 who underwent parathyroidectomy between 1997 and 2007 were retrospectively studied. The location and number of supernumerary parathyroids were reviewed, as well as whether cervical ultrasound and parathyroid SESTAMIBI scan (MIBI) were useful diagnostic tools. **Results:** In five patients (12.2%) a supernumerary gland was identified. In three of these cases (40%), the glands were near the thyroid gland and were found during the procedure. None of the imaging examinations were able to detect supernumerary parathyroids. In one case, only the pathologic examination could find a microscopic fifth gland in the thymus. In the last case, the supernumerary gland was resected through a sternotomy after a recurrence of hyperparathyroidism, ten years after the initial four-gland parathyroidectomy without thymectomy. MIBI was capable of detecting this gland, but only in the recurrent setting. Cervical ultrasound did not detect any supernumerary glands. **Conclusion:** The frequency of supernumerary parathyroid gland in the HPT1/MEN1 patients studied (12.2%) was significant. Surgeons should be aware of the need to search for supernumerary glands during neck exploration, besides the thymus. Imaging examinations were not useful in the pre-surgical location of these glands, and one case presented a recurrence of hyperparathyroidism.

Keywords: Multiple endocrine neoplasia type 1; primary hyperparathyroidism; parathyroid glands; ultrasonography; parathyroidectomy.

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterized by a germline mutation in the MEN1 gene that causes neoplastic changes in several endocrine glands, such as pituitary, pancreatic islet cells, and parathyroids[1,2]. Primary hyperparathyroidism (HPT1), an endocrine disturbance where an overproduction of parathyroid hormone (PTH) leads to elevated serum calcium, is usually the first manifestation of MEN1[1,3]. Most cases of HPT1 are sporadic (90%), but there are also some familial hereditary syndromes (10%), such as MEN1. Single parathyroid adenoma (85%) is the main cause of sporadic HPT1, while HPT1 with MEN1 generally presents an asymmetric parathyroid gland hyperplasia[3,4]. Parathyroidectomy is the treatment of the disease. Many authors recommend partial parathyroidectomy, in which part of or one small gland is left in the neck[5,6], and even selective parathyroidectomy of only abnormal macroscopic glands has been proposed[7]. Other authors prefer total parathyroidectomy with forearm autografting as the procedure of choice[8]. Irrespective to the type of parathyroidectomy, transcervical thymectomy seems to be advisable, due to the possibility of carcinoid thymic tumors, an extremely rare but aggressive neoplasm, which affects up to 8% of individuals with MEN1, being a cause of death in these patients with delayed diagnosis[3,4]. The second reason for this procedure is the embryological and anatomic relation between the inferior parathyroids and the thymus[9,10], which is a frequent site of ectopic parathyroid glands (up to 25% of cases) and possible supernumerary glands, when there are more than four parathyroids glands[11]. These supernumerary glands are an important cause of recurrent and persistent HPT1 after parathyroidectomy in MEN1 patients[11,12]. Thus, this study aimed to assess the frequency of supernumerary parathyroids in 41 Brazilian MEN1 patients with HPT1, their clinical importance, and the role of the diagnostic methods.

Methods

This retrospective study evaluates the frequency, anatomic presentation, and quantities of supernumerary parathyroids glands in 41 patients with HTP1 associated with MEN1 who underwent parathyroidectomy consecutively between 1997 and 2007 at the institution. These cases have been studied during the screening program for MEN1 that is being currently performed in this hospital[13,14]. They were diagnosed with MEN1 as they presented the proband with at least two of three tumors or with genetic tests in relatives of those patients, in accordance with international guidelines[15]. Whether the imaging examinations, namely cervical ultrasonography (USG) and parathyroid SESTAMIBI scan (MIBI), were effective to detect supernumary glands was reviewed. Whether prophylactic thymectomy could detect these glands was also studied.

Data collection on the patients' records searched the following parameters: age, gender, surgical procedure, and USG and MIBI reports. If available, these examinations images were compared with the macroscopic intra-operative findings, such as number, size, and location of the excised glands. The results of imaging were also analyzed when the glands were detected only in the routine histological examination of the thymus.

Results

Forty-one HTP1/MEN1 patients were operated. Nineteen were male and 22 were female. Their ages ranged from 19 to 73 years, with an average of 40.7 years.

In five patients (12.2%), a fifth parathyroid gland was found, and no patient presented more than five glands. Of these, only one patient was male and four patients were female. Their average age was 44 years (range: 32-59).

In the first case, a 32-year-old female, USG identified only one parathyroid gland, and MIBI found two hyperactive glands. Both findings were not correlated with the supernumerary parathyroid. The supernumerary gland was located between the upper right and lower right parathyroid glands, measuring 0.5 x 0.3 x 0.3 cm. In the second case, a female, 57 years old, USG identified only one parathyroid, and MIBI showed three hyperactive glands, but again none of the results was indicative of the supernumerary gland. The fifth gland was found medially between the left parathyroids, measuring 0.9 x 0.9 x 0.6 cm. In the third case, a female patient, 40 years old, had the same imaging parameters of case 2: only one parathyroid showed by USG and three hyperactive parathyroids in MIBI scan. Both examinations were not correspondent to the intraoperative finding of the supernumerary gland, which was just above the upper left parathyroid, measuring 0.6 x 0.4 x 0.3 cm. In these three cases the supernumerary parathyroids were found during the neck exploration, near the thyroid gland. In all these cases a clear separation of connective tissue was evident with the apparent topic parathyroids, which avoided the risk of the misdiagnosis of supernumerary gland by surgical splitting.

In the fourth case, a male patient of 59 years, none of the imaging studies or the neck exploration found a supernumerary gland, but the histological examination of the thymus revealed a microscopic supernumerary parathyroid.

The last patient, a 32 years old female, was submitted to a total parathyroidectomy with immediate autotransplantation in 1987. At that time, transcervical thymectomy was not a routine for these patients and USG was the only preoperative imaging available at the institution. Ten years after her first surgery (1997), she presented with recurrent HPT1. In the preoperative imaging examinations, MIBI scan suggested a mediastinal parathyroid gland, which was confirmed after resection requiring sternotomy. All cases are summarized in Table 1.

Table 1 – Cases of supernumerary parathyroids

Patient	Gender	Age	SPT found by USG?	SPT found by MIBI?	Localization of SPT
1	Female	32	No	No	Between RSPT and RIPT
2	Female	57	No	No	Right LSPT and LIPT
3	Male	59	No	No	Intratimic
4	Female	32	No	Ten years after first surgery	Mediastinal region
5	Female	40	No	No	Above LSPT

SPT, supernumerary parathyroid; USG, ultrasonography; TPT, topic parathyroid; RSPT, right superior parathyroid; RIPT, right inferior parathyroid; LSPT, left superior parathyroid; LIPT, left inferior parathyroid.

Discussion

Some anatomic studies showed a frequency of supernumerary parathyroid glands in the population ranging from 2.5% to 13%, frequently associated with the thymus or the embryological path of the lower parathyroids[9,10].

Two studies evaluated cases of supernumerary glands in secondary hyperparathyroidism (HPT2). In one study, 14.3% of patients had a fifth parathyroid[16]. The other reported supernumerary parathyroids in up to 30% of parathyroid operations, and when these glands were not excised, they were responsible for up to 32% of recurrent and persistent HPT2[17].

Three studies about HTP1 in patients with MEN1 related different proportions of supernumerary cases: 13%, more than 20%, and 30%, respectively[12,18,19].

The primary hyperplasia of this study presented an intermediary proportion of supernumerary glands in comparison to what was published in most anatomic studies and in clinical studies of patients with HTP2, and was lower than other studies of MEN1, as shown in Table 2. The difference between clinical and anatomic studies could be explained by the larger size of hyperplastic glands, or by the eventuality of its detection in recurrent cases that is not possible in cadaveric studies.

Table 2 – Proportion of supernumerary parathyroids in previous studies

Author / year	Proportion	
Akerström G et al.[10] / 1984	13%	(Anatomic)
Wang C[9] / 1976	2.5%	(Anatomic)
Arnalsteen L; Proye C[11] / 2003	30%	(HTP1/MEN1)
Gomes EMS et al.[16] / 2007	14.3%	(HTP2)
Lambert LA et al.[26] / 2005	2.7%	(HTP1)
Pattou FN et al.[17] / 2000	30%	(HTP2)
Hellman P et al.[18] / 1998	> 20%	(HTP1/MEN1)
Kraimps JL et al.[19] / 1992	13%	(HTP1/MEN1)
Present study	12.2%	(HTP1/MEN1)

Thompson et al. showed approximately 5% of supernumerary cases in an anatomical study based on clinical cases of HTP1 in general, including single adenomas and hyperplasias not related with MEN1[20]. This may be related to the fact that the vast majority of cases of solitary HTP1 are a single adenoma, where the excision of the affected gland is sufficient to resolve the disease, avoiding an extensive cervical exploration, reducing the chances of finding an extra gland[20].

A plausible explanation for a smaller proportion of supernumerary parathyroids in the present study of HPT1 versus that of HPT2 is the possibility of greater parathyroid growth stimulus in HPT2, which normally presents itself with more cases of supernumerary glands than general HPT1[20]. The clinical or genetic evaluation allows earlier diagnosis of HPT1/MEN1[21,22], which can determine the surgical treatment in early phases of HTP1 with less developed glands, where there was less time for the growth of mass and volume of these glands.

Among the 41 patients with HPT1/MEN1 studied, only one presented recurrent disease caused by a supernumerary parathyroid (2.22%). However, it should be noted that many of the present cases have less than ten years of follow-up. That is not enough time to rule out the possibility of recurrence, which occurs very late, in the authors' experience. The recurrence of HPT1 in MEN1 can occur later, when compared to HPT2.

The supernumerary parathyroid was found in the thymus in two of five cases. One was identified only through histology, and the other through the recurrent HPT1 after many years, confirming the possibility of asymmetrical and asynchronous hyperplasia of parathyroids in MEN1. In this view, studies with less than partial parathyroidectomy in which follow-up is inferior to five to ten years should be analyzed with caution.

The other glands were found during the neck exploration, not far from the other parathyroids. They were in an accessible and visible location for the surgeon. Thus, it is suggested that any node in the surgical field of the parathyroidectomy should be excised and sent for pathology testing in patients with MEN1-related HPT1. Irrespective to their size or macroscopic aspect, the resection of these

nodes may eventually show a supernumerary parathyroid, although in most cases a lymph node is reported by the pathologist.

All cases have maintained the location pattern of these glands, always reinforcing the need of thymectomy due to high incidence, and the need for a careful neck exploration during surgery. Arnalsteen et al., in two studies about recurrent HPT1, found that supernumerary parathyroid was responsible for 51% of cases recurrent HTP1 in asymmetric hyperplasia, including cases of MEN type 1[10,11].

As in other studies, in the present study imaging examinations, such as USG and MIBI, were not effective for localizing supernumerary glands at the initial operation[11,16]. In fact, many supernumerary glands were small and very difficult to identify by current methods. The success of MIBI scan of hyperactive parathyroids has a close relationship with the size and histological features of these glands, but it is useful to suggest an ectopic gland, especially in the mediastinal region[23-25]. One of the present cases, as well as a report found in the literature[25], may serve as example, because ten years after the first surgery, during investigation of the recurrent disease, only the MIBI scan detected the supernumerary parathyroid in the mediastinal region. Another method now widely used to detect a possible supernumerary gland is intra-operative serum PTH. This method seems to fail in tracking supernumerary glands in MEN1, because the PTH secretion ability of a gland depends on its size. Thus, the small size of most supernumerary glands, still in initial hyperplasic process, may prevent the production of PTH in sufficient quantity in order to affect the pattern of PTH decay[8]. Notwithstanding, it is thought that intraoperative PTH should be employed in these cases if available. Intraoperative PTH can suggest a hyperfunctioning parathyroid, but it would not be a reliable indicator of microscopic glands. It is hard to predict if or when a small thymic parathyroid gland will cause recurrent HPT. High rates of recurrence (64% at median follow-up of four years) after parathyroidectomy in MEN1 have been reported[26]. The persistence of an elevated PTH level after successful four-gland resection is strongly suggestive of a hyperactive supernumerary parathyroid gland, which should be searched for before closing the wound. On the other hand, it would help to stop the extensive exploration when less than four glands were identified, if a significant fall of PTH is demonstrated.

As for the benefit of thymectomy, which is routinely performed at this institution for HPT in MEN1 cases since 1997, despite not being part of this study, it is worth noting that another patient followed at the institution, previously submitted to a parathyroidectomy without thymectomy, developed a thymic carcinoid tumor, five years after the parathyroidectomy. Thymectomy is not routinely performed for secondary or tertiary HPT at the institution. No risk of carcinoid tumor is present in renal cases. Anatomic bases for supernumerary glands are apparently indistinct regarding MEN1, HPT, and renal HPT. However, clinical behavior seems to be not comparable: in the authors' experience, the recurrence rate is low in renal HPT, and in most cases related to autotransplantation. These examples illustrate and reinforce the potential benefit of thymectomy in all cases of HPT1 associated with MEN1. In other conditions, such as renal related hyperplasia, the risk of extra surgical time and the potential risk to the innominate vein related to this strategy must be considered.

Conclusions

Supernumerary parathyroid glands in HPT1 with MEN1 were found in 12.2% of the present cases. Surgeons must be aware of the possibility of also finding these glands in the neck during the procedure, although many of them are in the thymus. Imaging studies were not helpful in locating supernumerary glands before the first surgery in HPT1 with MEN1, but this aspect should not discourage their use, as ectopic glands are also a considerable clinical problem in these patients.

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