Original Articles

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Thyroid and Thymic Exeresis in Surgery of Hyperparathyroidism

M.R. Diaconescu[1], M. Glod[1], I. Costea[1], M. Grigorovici[1], S. Diaconescu[2]

[1]IV[th] Surgical Department, "Gr. T. Popa" University of Medicine and Pharmacy, Iaşi, Romania
[2]V[th] Pediatric Department, "Gr T Popa" University of Medicine and Pharmacy Iaşi, Romania

Rezumat

Exereze tiroidiene și timice în chirurgia hiperparatiroidismului

Introducere: Conexiunile anatomice şi embriologice intime dintre tiroidă, glandele paratiroide şi timus determină prezența unor frecvente şi variate asocieri lezionale identificate în cursul diverselor explorări chirurgicale pentru tratamentul hiperfuncției paratiroidiene (Hp).
Material și metodă: Studiul nostru retrospectiv cercetează incidența, formele clinice, histologia şi atitudinea chirurgicală adoptată în leziunile tiroidiene şi timice coexistente într-o serie de 82 cazuri consecutive de Hp operate în ultimele trei decenii. Au fost revizuite datele demografice, cele clinice şi biochimice, investigațiile imagistice ca şi protocoalele operatorii şi rezultatele histopatologice.
Rezultate: Între 1984-2013 82 observații de Hp: 57 femei şi 25 bărbați, raport 2,3/1 având intre 15-72 (medie 46,5) ani au fost operate în clinica noastră. Am înregistrat 20 cazuri de Hp primar şi 62 cazuri de Hp renal (27 secundar şi 35 terțiar). Au fost practicate 32 de exereze tiroidiene concomitente (2 tiroidectomii subtotale, 12 lobectomii, 8 rezecții atipice, şi 10 biopsii diagnostice) pentru guşi (multi)nodulare sau leziuni minime ("minute") uni- sau bilaterale. Examenul microscopic a evidențiat guşă coloidă în 11 cazuri, 3 adenoame foliculare, 5 hiperplazii nodulare, 6 tiroidite, 3 microcarcinoame papilare şi 4 aspecte normale. Excizia țesutului fibroadipos retromanubrial a pus în evidență un timom benign nonmiastenic, un chist timic şi resturi timice în 6 situații. Morbiditatea în aceste exereze extinse nu a fost semnificativ crescută comparativ cu intervențiile limitate doar la leziunile paratiroidiene.
Discuții şi concluzii: Evaluarea meticuloasă pre- şi intraoperatorie a tuturor observațiilor de Hp a permis actuala orientare către chirurgia minim invazivă a acestor leziuni în dauna explorării bilaterale tradiționale, preferință care creşte totuşi riscul potențial al ignorării unor leziuni tiroidiene sau timice semnificative. Oricum chirurgul dedicat acestei patologii trebuie să fie avizat asupra posibilității de a fi confruntat cu asemenea leziuni sincrone şi determinat pentru a practica o operație completă într-un singur timp.

Cuvinte cheie: hiperparatiroidism, tiroidă, timus, coexistență lezională

Abstract

Background: Owing to close anatomical and embryological connexions between the thyroid, parathyroids and thymus, manifold coexisting pathology can be identified during the surgery of hyperparathyroidism (Hp).
Material and Methods: In this retrospective study we report the incidence, clinical forms, histology and management of thyroid and thymic synchronous lesions encountered in a series of 82 consecutive patients with various types of Hp operated on in the last three decades. Demography, clinical records, biochemical data, imaging procedures, pathology reports and surgical protocols were revised.
Results: Between 1984-2013, 82 cases of Hp, 20 primary and

Corresponding author: Smaranda Diaconescu, MD
V[th] Pediatric Clinic
"Sf Maria" Emergency Clinical Hospital
62, Vasile Lupu Street, 700309, Iași, Romania
E-mail: sdiaconescu@mail.umfiasi.ro

62 renal (27 secondary and 35 tertiary), 57 women and 25 males (sex ratio: 2.3/1) of 15-72 (mean 46.5) years, underwent surgery in our clinic. Concomitant thyroid exereses were performed in 32 patients (2 subtotal thyroidectomies, 12 lobectomies, 8 atypical resections and 10 diagnosis biopsies), for uni- or bilateral (multi)nodular goiters or different "minute" lesions. Pathology showed 11 colloid goiters, 3 follicular adenomas, 5 nodular hyperplasias and 6 thyroiditis cases, 3 papillary microcarcinomas and 4 specimens with normal thyroid tissue. Excision of the fibrofatty retromanubrial tissue in total parathyroidectomies for renal Hp (19 cases) revealed one nonmyastenic thymoma, one thymic cyst and thymic remnants in 6 patients. Morbidity in these extended operations was not significantly increased, comparing to the parathyroid exploration alone.
Discussions and Conclusions: Meticulous pre- and intraoperative evaluation in all cases of Hp enables the actual shift from bilateral neck exploration to minimally invasive surgery, increasing however the potential risk of missing thyroid or thymic coexistent significant lesions. The surgeon dedicated to this pathology must be aware of the possibility of encountering such synchronous association and make generous efforts towards their complete cure in a single operation.

Key words: hyperparathyroidism, thyroid, thymus, coexisting lesions

Background

Close anatomical connexions between the parathyroid glands, the thyroid, as well as their common embryological origin with the thymus, create additional difficulties in the identification and optimal surgical treatment of cases of primary and renal Hp coexisting with benign or malignant lesions of the two other cervical endocrine structures.

The high incidence of thyroid pathological conditions – especially of nodular lesions – as well as of different varieties of Hp revealed increasingly frequent simultaneous lesions of the both glands, preeminently in endemic areas (1,2,3,4,5).

Similar growth in the number of cases of renal Hp, of which a significant percentage imposed a surgical solution, often determined the excision of the retromanubrial fibrofatty surrounding tissue, where the ectopic or supranumerary parathyroids and also the sometimes organized thymic cellular rests are at times located (6,7).

Surgeons must always evoke the possibility of such pathological coincidences which require a sustained pre- and intraoperative exploration completed by pathological examination in order to complete lesional inventory and an appropriate treatment of both lesions during primary surgery, avoiding risks of iterative operations which can generate a high percentage of complications.

The purpose of the study is to present and analyse our experience in the incidence, clinical and lesional circumstances of these associations – often fortuitous, as well as the therapeutic attitude adopted throughout the literature data.

Material and Method

Our series included 82 consecutive cases of primary and renal (secondary and tertiary) Hp operated over a period of three decades (1984-2013).

Clinical data were consulted for:

- osteoarticular manifestations: pain, osteoporosis, fractures and bone cysts;
- urinary manifestations: multiple, bilateral and recurrent lithiasis, chronic renal failure under hemodialysis regimen;
- also neuromuscular, psychoneurotic, cardiovascular and digestive manifestations (most of them also present both in hyperparathyroidism and in goiters and especially thyrotoxicosis).

Biological data: abnormal levels of iPTH, total/seric calcium, phosphorus, alkaline phosphatase.

Imaging data: the real time ultrasound did not not always reveal all parathyroid lesions i.e. ectopies, supernumerary or less than 5 mm glands and did not differentiate between benign and malignant lesions.

Parathyroid scintigraphy with tetrofosmin was accessible solely in the last period, but thyroid scintigraphy was recommended only sporadically.

Pathology exams (FNAB echoguided or not), were useful in some cases, certifying benignity. Frozen section (FS) confirmed the tissue diagnosis, however being sometimes inconclusive for differentiating benign from malignant lesions; therefore paraffin section (PS) remained the decisive investigation.

Treatment was adapted to the diagnostic and the encountered lesional aspect, being modulated by FS, aiming the optimal removal both of the parathyroid hyperfunction and its clinical effects, and also of the coexistent thyroid pathology, therefore ensuring an effective cure of the most negative component (thyroid or parathyroid carcinoma).

In the 20 cases of primary Hp (17 adenomas, one parathyromatosis and two carcinomas) we resorted to simple exeresis of the adenoma-bearing gland in 16 cases, with the exception of one patient initially considered a renal Hp, who underwent a subtotal parathyroidectomy.

Also, four parathyroid lesions resected "en bloc" with the thyroid lobe were performed for:

- intrathyroid parathyroid adenoma, "suspect" but benign at paraffin section;
- one case of parathyromatosis for Hp recurrence at 6 years after an extramural excision of a parathyroid adenoma; surgical re-exploration detected multiple micronodules (2-3 mm), benign on FS, but PS identified a folliculo-papillary thyroid microcarcinoma (*Figs. 1, 2*)
- two parathyroid carcinomas – the first one evident due to tumor volume and macroscopic aspect, excessive level of biological constants and intensity of clinical syndrome, the second, (new lesion?) also a relapse at 4 years after removal of a certainly benign ipsilateral adenoma.

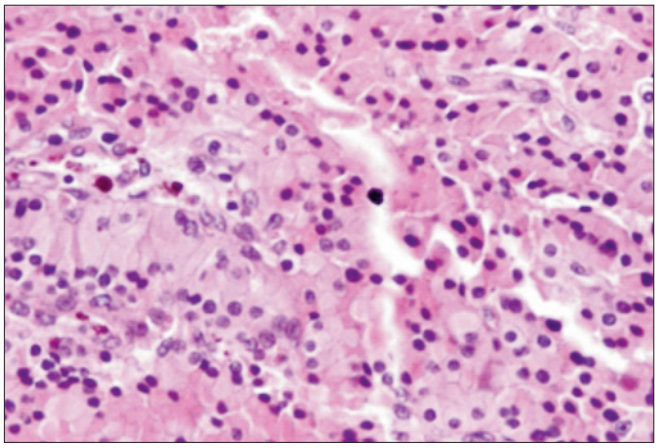


Figure 1. *Parathyroid micronodular hyperplasia (HE x 200)*

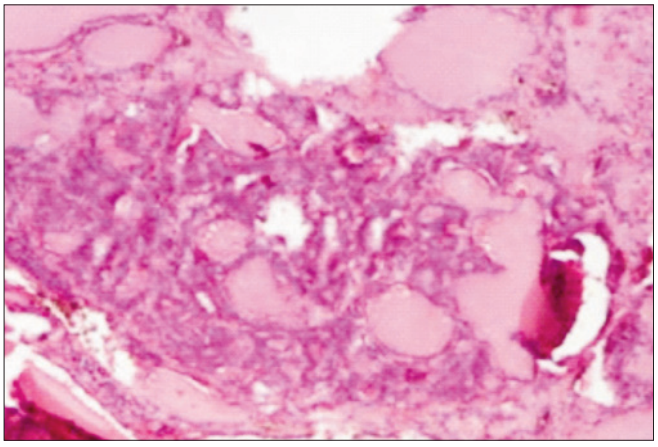


Figure 2. *Folliculo-papillary thyroid microcarcinoma (HE x 20)*

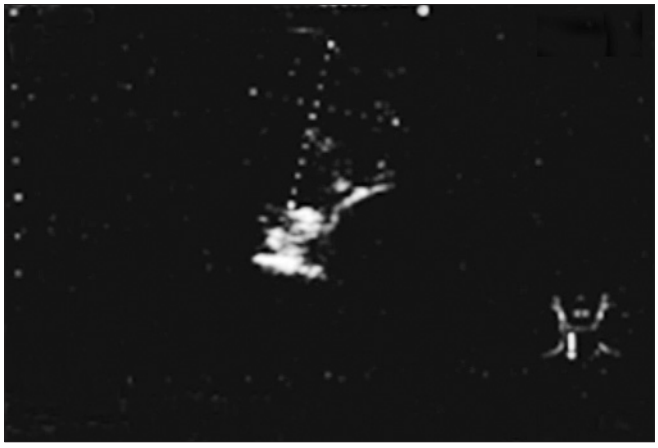


Figure 3. *Ultrasonography: left "thyroid" nodule*

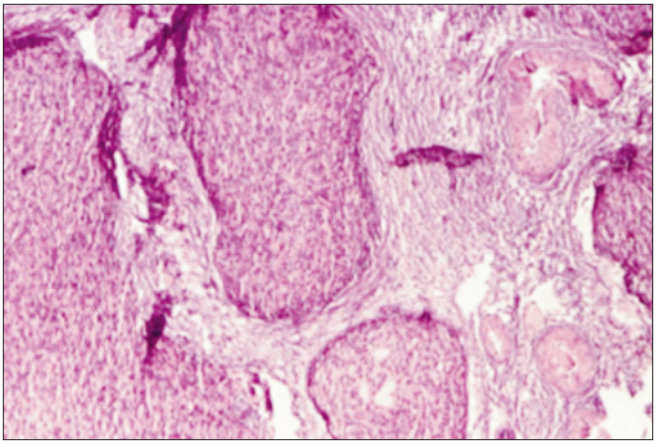


Figure 4. *Parathyroid carcinoma (HE x 20)*

Otherwise concomitant with adenoma excision a near-total thyroidectomy for benign multi-nodular goiter (40 g), a total lobectomy with isthmusectomy for "cold" suspect (but benign at PS) nodule, three "tactical" lobectomies for intra-lobar located adenoma (one case) and with a deep retrothyroid location (two cases) and finally, two enucleoresections for apparently innocent nodules intraoperatively discovered, have been practiced. Pathology stated the diagnosis of colloid goiter (one case), nodular hyperplasia (2), chronic unspecific thyroiditis (2) and normal thyroid tissue (1).

In the 62 cases of renal Hp 28 subtotal (4 incomplete) parathyroidectomies and 34 total parathyroidectomies (7 with forearm glandular autotransplant), 21 thyroid accompanying exereses were performed:

- one subtotal thyroidectomy for a voluminous multi-nodular bilateral goiter (55 g), but also in order to identify two nowhere to be found inferior parathyroid glands; conversely a 5 mm Ø infiltrative thyroid papillary microcarcinoma was discovered; patient refused re-intervention but after 4 years during which he was subjected to irradiation and hormonal therapy he is still alive, continuing hemodialysis and medical treatment of persistent Hp;
- 4 lobectomies – two total – the first one for a papillary thyroid microcarcinoma, the second one for a 38 mm Ø left inferior parathyroid carcinoma accompanying hyperplasia of other glands (*Figs. 3, 4*) and respectively two subtotal for a unique nodule with certain benignity or to tactical purpose for highlighting small in size and abnormally localized glands;
- 6 lobar atypical resections and two enucleoresections, also for biopsy confirmed benign nodular lesions.
- 10 biopsies with benign aspects and normal thyroid tissue.

Overall, aside from the two thyroid microcarcinomas and the fortuitously discovered parathyroid carcinoma, paraffin section established the diagnosis of colloid goiter (6 patients), follicular adenoma (3), nodular hiperplasia (3) and thyroiditis (4).

Among the interventions for renal Hp in 19 cases we also extended the exploration to the fibrofatty retromanubrial tissue including thyrothymic ligament routinely excised in 12

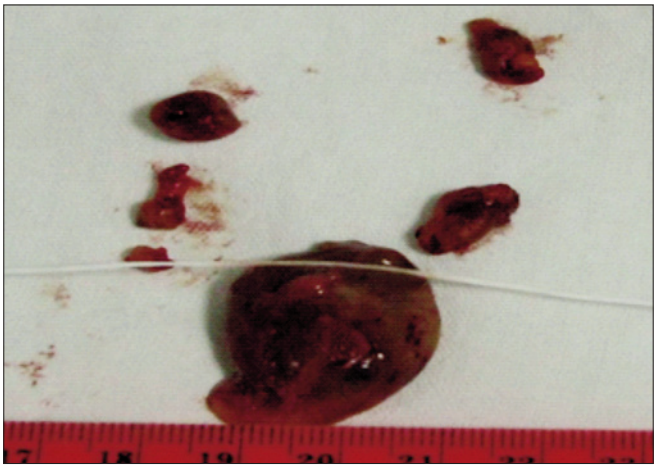


Figure 5. *Operative specimen: 4 parathyroids & thymoma*

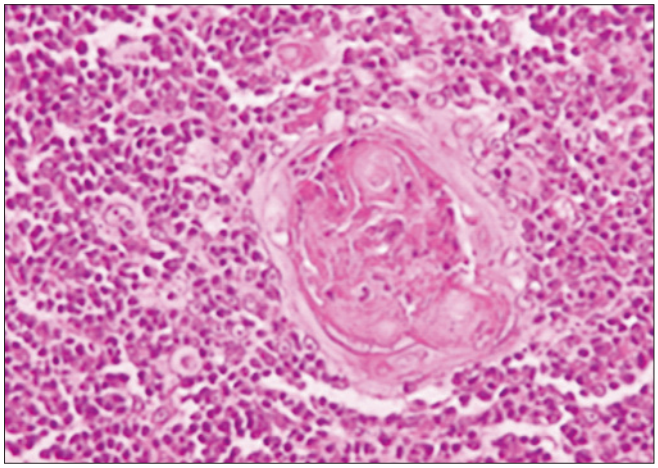


Figure 6. *Microscopy: benign thymoma (HE x 100)*

cases and ectopic glands searched in 7 cases, descended glands being found in 5 of these. In another observation through this manouver we identified the only presence of a 5th gland. Fibrofatty tissue exploration highlighted in addition a benign nonmyasthenic thymoma, a flattened thymic cyst and in other 6 cases thymic cellular rests, exploration proving to be opportune. (*Figs. 5, 6*)

Our mortality rate was zero and the number of complications was low, i.e. one hematoma lodge that had to be drained, one recurrential paresis and two episodes of hypocalcemia which yielded after vitamin D and calcium medication. However morbidity was significantly higher than in cases that underwent only parathyroidectomy alone ($P > 0,5$). Through regular checks and correspondence with patients or centers who guided them we achieved a high coverage of cases monitoring, 41 of them being alive at 3 – 208 months after surgery, three having died due to progression of renal failure and 18 being lost to follow-up

Discussions and Conclusions

Coexistence of thyroid and thymus lesions diagnosed preoperatively or discovered during surgical treatment of main anatomoclinical forms of Hp is characterised by variability in incidence and especially aspects of encountered lesions. Increased frequency of thyroid pathology, especially of nodular goiter mainly in endemic areas, but also of symptomatic and particularly asymptomatic Hp – or even of renal Hp due to increasing number of patients undergoing hemodialysis - explain the more often signalled simultaneous presence of both endocrine lesions in same patient.

First mentions of Hp associated with thyroid pathology belong to Noble (1932) and Wood (1934), subsequent studies estimating the frequency of this lesional concomitance between 20 - 70% and even up 83.4% in the endemic goiter territories. (1,2,3,4,5,11,12,13,14,15,16,17)

Classical pairing of parathyroid and thyroid lesions in MEN syndromes should be mentioned from the beginning. Thereby MEN I reunites parathyroid hyperplasia determining Hp, which is present in 80 – 90 % of cases, with both a pancreatic component (including the redoubtable Zollinger Ellison syndrome) and one pituitary, to which thyroid adenoma and even thymic carcinoids are rarely added. (18)

More obvious is the presence in MEN II A of medullary thyroid carcinoma, which constitutes the dominant clinical and prognostic lesion, followed in importance by pheochromocytoma, the parathyroid component (hyperplasia) being less expressed in the syndrome pattern.

Therefore total thyroidectomy (sometimes practiced prophylactically) becomes the essential surgical gesture, to which parathyroidectomy is added, usually performed concomitantly, subordinated to the radical nature of thyroid exeresis. (19,20)

Aside from nodular goiters, we must add mainly unique or multiple benign hyperplasia or follicular adenomas, presence of inflammatory lesions – unspecific chronic "accompanying" or lymphoplasmocitary thyroiditis (up to 42 % of cases), but also the rare observations of thyrotoxicosis i.e. Basedow's disease, toxic adenoma. (12,21,22,23,24,25)

Significant however appeared the increasing proportion of thyroid (micro)carcinoma cases discovered during interventions for hyperparathyroidism estimated between 3 – 5 % in early studies, but reaching 36-37.2 % in recent papers, superimposable to that found in our experience. (26,27,28, 29,30)

Although a more frequent occurrence of thyroid carcinoma in PHp compared with renal Hp was suggested, it seems that the distribution of these malignant lesions is equal between the two forms of parathyroid hyperfunction. (31,32,33,34,35)

Papillary thyroid carcinoma is preponderantly registered in more than 95 % of cases. The presence of a thyroid component can be appreciated clinically – solitary nodule or multinodular goitre detected in 23 % of cases, and rarer thyrotoxic features - but in the majority of patients their attendance is discreet (commune neurovegetative signs of both endocrinopathies) or even absent (infranodular, microscopic lesions). It must also be emphasized that asymptomatic hyperparathyroidism is more

common in cases with a thyroid associated component.

Under these conditions, paraclinical examination of all cases of Hp must be completed with the dosing of TSH, thyroid hormones and antibodies, but also thyrocalcitonine, while usual imaging should eventually include thyroid scintigraphy in cases of sonographic suspicions.

Thyroid lesions impose a standard anatomical and functional exploration (ultrasound, scintigraphy), but especially morphological examinations (FNAB, frozen and paraffin sections).

Operative attitude implies an appropriate simultaneous removal of both lesions: adenomectomy, subtotal or total exeresis for parathyroids, respectively conservative or radical thyroid surgery, the more reduced one being a total lobectomy with isthmusectomy for suspect or incidentally discovered malignant nodules and near total or total thyroidectomies for bilateral and especially preoperatively diagnosed carcinomatous lesions.

Risks and complications of this operative strategy appear slightly higher than parathyroidectomies or thyroidectomies performed separately, but undoubtedly lower than those encountered in reinterventions (2,5).

Concerning routine resection of retromanubrial tissue recommended by some specialists in the surgery of RHp, we suggest an eclectic approach in cases where the inferior parathyroid glands are not identifiable; exploration can bring the pleasant surprise of discovering an ectopic or supernumerary gland, but also of some tissular remnants or even constituted lesions of the thymus.

Presence of benign or malignant, nonfunctional or functional thymoma is a rarity, concurrence with hyperparathyroidism being recorded in only 5 cases (38,39, 40,41).

Single observations of ectopic production of PTH by a thymoma, thymic carcinoid associated with hereditary hyperparathyroidism or component of MEN I, all emphasized the need for dosing as many markers as available in these bizarre pathologic associations. Thymic cysts are also uncommon, but there are mentions of intrathymic localization of parathyroid functional cysts (42,43,44).

Conclusion

Proximity in a limited cervical territory of three endocrine organs with close anatomical and embryological reports, can provide amazing lesional coincidences with variable incidence, to be known by surgeons involved in the field.

Conflicts of interest

All authors declared there is no conflict of interest.

Authors contributions

MR Diaconescu: conception and design of study, performed the surgery. M Glod & I Costea: members of surgical team, analysis of data. Mirela Grigorovici: expertise in pathology. Smaranda Diaconescu: drafted the study and revised it for intellectual content.

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