

Unusual Malignant Tumors of the Thyroid Gland

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Rezumat

Tumori maligne neobișnuite ale glandei tiroide

Introducere: Deși situate printre ultimele în ierarhia neoplaziiilor maligne, cancerele glandei tiroide (CT) constituie cele mai frecvente tumori ale sistemului endocrin. Peste 90% dintre aceste leziuni sunt cancerele derivate din epiteliul folicular care au un prognostic favorabil, restul tumorilor (medulare, nediferențiate, limfoame, sarcoame etc) având în general o evoluție rapidă și supraviețuiri limitate.

Material și metodă: Într-o serie retrospectivă de 464 tireopatii tratate în serviciul nostru am înregistrat 72 CT (15,5%): 57 cancere epiteliale (34 papilare, 15 foliculare și 8 mixte), 2 cancere medulare, 9 cancere anaplazice și respectiv câte un caz de CT slab diferențiat (insular), metastază tiroidiană a unui cancer pulmonar și un limfom malign. Eliminând majoritatea varietăților habituale am selecționat pe baza unor criterii taxonomice proprii un grup de 36 observații cu caractere clinice, histologice, evoluție și prognostic sau coexistențe patologice neobișnuite.

Rezultate: Din punct de vedere clinic am disociat în cadrul tumorilor bine diferențiate 7 CT oculte, tot 7 cu adenopatie “precesivă” și 11 CT asociate cu tirotoxicoză. Toate au beneficiat de exereze adaptate în care prezenta cancerului a impus extensia operației. Cancerule medulare, cel insular și formele nediferențiate s-au dovedit leziuni agresive, greu de controlat terapeutic și cu supraviețuiri reduse în ciuda unor

intervenții uneori extinse, administrării de 131-I ori radio- și chimioterapie. În aceeași categorie încadrăm și asocierile dintre două tipuri de CT, dediferențierea histologică ca și coexistența neoplaziei cu alte leziuni cervicale endocrine sau nu. În toate aceste situații dogma tiroidectomiei totale nu a putut fi totdeauna aplicată recurgându-se la terapii complementare. Rezultatele au fost disociate înregistrându-se vindecări stabile în leziunile oculte, cele hiperfuncționale sau cu coexistențe patologice dar și numeroase recidive și reintervenții cu supraviețuiri limitate în cazurile cu diferențiere histologică redusă sau absentă. Unele leziuni au fost inoperabile.

Discuții și concluzii: Conștientizarea existenței acestor eventualități mai puțin obișnuite dar nu de excepție de către clinician, chirurg și morfopatolog, poate contribui major la diagnosticul și tratamentul lor adecvat. Progresele recente în cunoașterea carcinogenezei moleculare și rezultatele promițătoare ale trialurilor chimioterapeutice “țintite” oferă noi perspective în managementul formelor avansate și metastatice de CT. Chirurgia rămâne însă principala metodă terapeutică a CT.

Cuvinte cheie: cancer tiroidian, varietăți neobișnuite, chirurgie, tratament complementar

Abstract

Background: Although situated on the last places among the statistical hierarchy of human malignancies, thyroid cancers (TC) are the most common tumors of the endocrine system. Follicular epithelium neoplasms account for more than 90% of these lesions with a favourable prognosis, while resting tumors (medullary, anaplastic, lymphoma, sarcoma etc) generally present a rapid unfavorable evolution with a low rate of survival.

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Patients and methods: In a series of 464 thyropathies personally treated, 72 cases of TC (15.5%) were identified. Fifty-seven patients presented epithelial TC – 34 papillary variant, 20 follicular variant and 8 mixed forms. Alongside these there were two medullary TC, 9 anaplastic TC and insular TC, and primary lymphoma and metastasis to the thyroid of a lung carcinoma each single case. Four cases have been described in patients who were aged 2-6 years at the time of the Chernobyl disaster. Out of the common types, based on our own taxonomic criteria, we selected a group of 36 TC with unusual clinical, histological and behavioural characteristics or particular pathological associations.

Results: Seven cases of occult TC, 7 cases with precessive adenopathy TC and 11 patients with TC associated with hyperthyroidism were registered. All of them underwent adapted thyroidectomies in which the presence of cancer was decisive for the extent of surgery. Medullary, insular and anaplastic TC were the most aggressive lesions and even extended surgery and complementary therapy failed to improve the prognosis of these patients. In the same category we included the cases presenting the coexistence of two TC types, pathologic dedifferentiation in recurrences and concurrent presence of another endocrine or nonendocrine cervical lesion. The “surgical dogma” of total thyroidectomy cannot always be respected, so complementary therapeutic solutions must be applied. Results were complex, registering steady recoveries in occult, hyperfunctioning and even in coexisting pathological lesions, but many recurrences and reinterventions with poor survival rates (a few weeks up to 2 years) in cases with reduced or absent histologic differentiation were also noted. Some lesions were inoperable.

Discussions and conclusions: Increasing clinician, surgeon and pathologist awareness of these distinct, but not rare anatomic-clinical contingencies could contribute to their adequate diagnosis and treatment. Recent progress in knowledge of molecular carcinogenesis and promising successes of targeted chemotherapy trials with new drugs offer promising perspectives in the management of advanced or metastatic TC. Surgery still remains the cornerstone treatment for thyroid cancers.

Key words: thyroid cancer, uncommon types, surgery, complementary therapy

Background

Thyroid malignancies constitute a rare group of lesions ranking 22th in the hierarchy of human malignancies but, at the same time remaining the most common cancers of the endocrine system.

The thyroid gland is a complex organ composed of a multitude of cellular types: epithelial follicular and parafollicular (C) cells, along with connective, lymphoid, vascular or nervous cellular elements, also sometimes presenting residual or ectopic nests of parathyroid, thymic or thyroglossal duct tissues. All of

these structures are able to give rise to a vast number of inherited or acquired, benign or malignant tumoral lesions of different origins, clinical and pathological features and capricious natural history and behaviour.

The main classification and staging systems proposed by WHO and AJCC assigned four main types of thyroid cancers (TC): papillary, follicular and anaplastic tumors (all of them originating in epithelial follicular cells) and medullary cancer (originating from parafollicular cells). Adding to these are some peculiar variants such as lymphomas, sarcomas and other uncommon forms.

This synoptic taxonomy included under the broad term “uncommon TC” a great and puzzling number of lesions differentiated by their incidence, genetic origin, microscopic and molecular structure, clinical picture and prognostic, pathologic associations or ectopic locations, all all requesting multidisciplinary therapy.

Based on personal experience and abundant literature we outlined some groups of more or less atypical TC imposing rational diagnosis efforts and sometimes individualised management, evaluating the use of new treatment strategies, hopefully aiming to improve clinical outcome in the next several years.

Patients and Methods

From a personal retrospective series of 464 cases operated on for different thyroid conditions, we registered 72 patients representing 15.5 % of thyroid carcinomas (tenfold as in international statistics): 39 papillary, 20 follicular and 8 mixed, 2 medullary, 9 anaplastic, and poorly differentiated (insular) TC respectively, a thyroid lymphoma and a thyroid metastasis from a lung carcinoma - one case of each. None of the patients had a history of previous neck irradiation or radioiodine therapy. The majority of patients underwent surgery. FNAB, frozen section and histopathology were performed systematically. Clinical records, pathological sections, imaging and operative protocols, as well as follow-up dates were reviewed.

Results and Discussions

The first uncommon clinical entities are the occult and infra-clinical thyroid carcinomas.

Occult thyroid carcinomas (OTC) are defined as subcentimetric lesions (< 1 cm ϕ) (minute cancers even < 5 mm ϕ) habitually detected incidentally on ultrasound or CT, found by FNAB or finally after the exeresis of different benign thyroid lesions or neck lymph nodes, or in the presence of clinically apparent metastases. OTC is somehow practically synonymous with papillary microcarcinoma, although all other varieties (including anaplastic in its most precocious stage) can be discovered at their minimal dimensions. Most of these lesions “hibernate” and do not become clinically apparent, being discovered during necropsy studies with notable differences in range, from 0.01 to 35.6% (!).

The reputed “innocence” of OTC is an argument in choosing the appropriate limited surgery (total lobectomy with

isthmusectomy) and close follow-up leads to excellent survival rates, greater than 96% at 10 and 15 years.

On the other hand, risk stratification can identify small groups of PMC with aggressive biological behaviour determined by genetic predisposition, multiplicity, specific BRAF mutations, overexpression of protein S100 A4 or Cyclin D1, all being extremely valuable arguments for the indication, moment and extension of surgery, as well as for the need of radio-iodine complementary therapy. (7,8)

In our series we encountered 7 OTCs (6 papillary and one follicular – Fig. 1) fortuitously identified in a toxic adenoma, in three “innocent” nodules and in three cases of hyperparathyroidism (one parathyromatosis and two renal forms). In 5 cases total lobectomies were performed and in two cases (one in the follicular tumor) a completion thyroidectomy succeeded the initial conservative exeresis of the small nodule. (8)

In the same category we also included precession (prevailing) adenopathy (Fig. 2) without any identifiable thyroid tumor, reported in different percentages in the literature, ranging between 10-50%. It is the clinical expression of a specific propensity mainly of PTC, but also of other types of TC (follicular, medullar, anaplastic and insular as in our sole case) in the lymphatic system. Of course lymph node invasion involved at first the cervical lateral compartment, where it is earlier and more easily discovered, but inaugural adenomegaly can also be described in the central or contralateral territories. Clinical findings depend on the volume and location of the node, and on subhyoidian musculature and neck fat development. What is striking in these circumstances is the clinical and imaging absence of any thyroid or other type of neck lesions, which adds to the inconclusive results of FNAB or “picking” limited biopsy performed frequently in unspecialized units, leading to diagnostic confusions and delays. The ideal algorithm in these situations included multiple guided ultrasound, eventually repeated FNAB, cervical CT scan, MRI and highlighting of biological tumor markers. (10,11)

A consensus regarding the extension of thyroid exeresis exists in these cases, the recommendation being for total lobectomy with isthmusectomy at least, but near total or total thyroidectomy have become the routine procedures. In opposition, the lymph node surgical sequence respects the principle of systematic compartment-oriented neck dissection balanced between lateral cervical exclusively or more extensive (central, both lateral and central or contralateral) nodal excision (argued by the fact that nodal deposits are already a

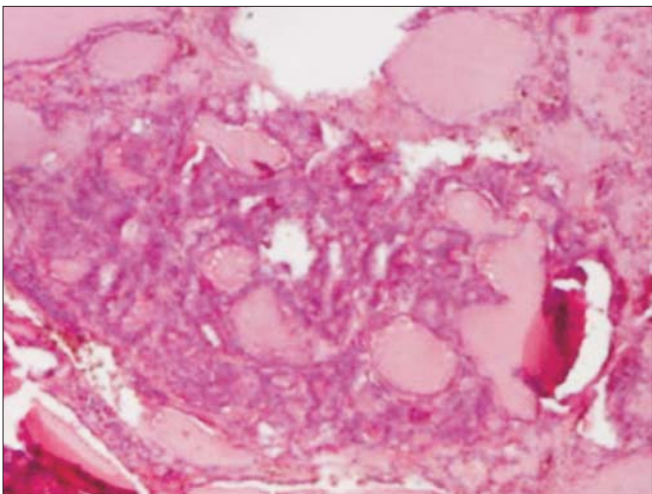


Figure 1. Folliculo-papillary microcarcinoma

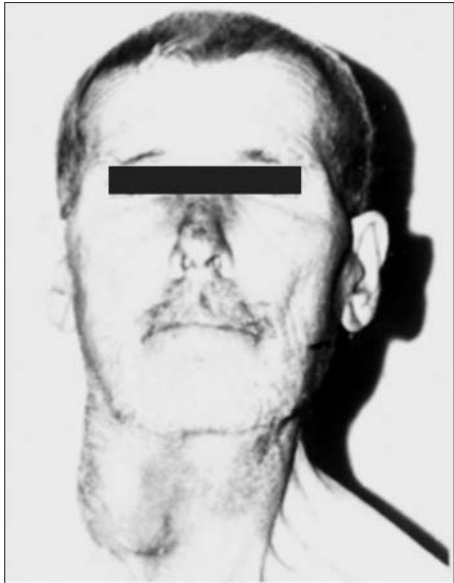


Figure 2. Thyroid carcinoma with a precessive adenopathy

sign of multicentricity). There is also prophylactic neck dissection. Radioactive iodine therapy (when necessary) and TSH-suppressive hormonal administration favourably influenced the prognosis. (10)

Below is a Table 1 with our cases [one can notice that two

Table 1.

1	PN ♀ 34	T3N2Mx cold nodule	1/biopsy 2/ TT+RND	Pap&Fol 131I&T4 > 5 y
2	CE ♀ 28	T1N2Mx cold nodule	1/biopsy 2/ TT+MND	Fol&Pap “ > 5 y
3	ES ♀ 30	TxN1Mx*	1/biopsy 2/ TT +MND	Pap “ > 5 y
4	SG ♂ 63	T1N2Mx	TT+MND + N sclv	Fol&Pap “ ?
5	BV ♀ 16	T1N2Mx cold nodule	nearTT + MND	Pap - > 5 y
6	GI ♂ 59	TxN2Mx*US nonhomogenous	TT+ MND	Ins - > 3 y
7	SI ♂ 58	T1N2Mx cold nodule	1/neck dis 2/ TT	Undiff Rot ?

to notice that two of them (*) are common with OTC



Figure 3. *Graves' disease*

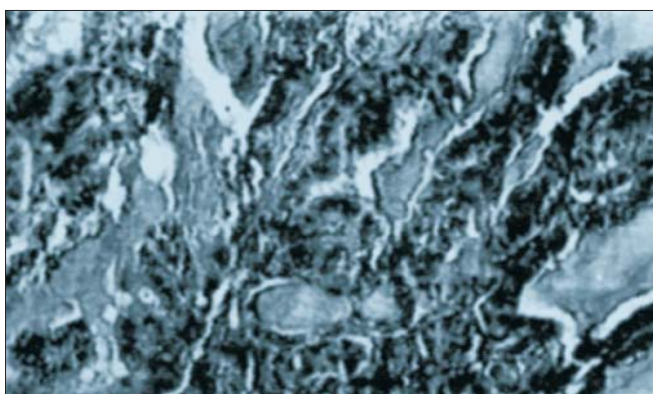


Figure 4. *Papillary TC associated with areas of hyperfunction*

of them (*) are common with OTC].

Thyrotoxicosis was axiomatically considered insurance against TC, but according to recent literature, the incidence of the concurrent apparition of both entities seems to be increasing, even if their pathogenic relationship still remains obscure. Two main clinical and pathological types of this coexistence are described. The most frequent one included patients with classical forms of thyrotoxicosis associating unsuspected occult lesions (Fig. 3, 4), but also grossly evident TC. The second category is composed of documented cases of thyroid carcinomas with simultaneous presence of clinical, biological or histological features of thyroid hyperfunction. (12,13,14)

In the former group we observed 10 patients (9 ♀ and one ♂) aged 28-63 years operated on for Graves' disease (3 cases), toxic nodular goitre (4) and toxic adenoma (3), harbouring 6 papillary microcarcinomas and 4 thyroid malignant nodules diagnosed histologically among or inside another abnormal pathology. None of these cases had received previous head or cervical irradiation. Each patient underwent clinical, bio-

chemical, scintigraphic and ultrasound evaluation. Surgical attempt consisted in 4 lobectomies, 5 near total and one complete thyroidectomy. Only one case of overt thyrotoxicosis caused by a thyroid carcinoma can be described in our experience: a 54-year-old female with a long-standing multinodular, large, firm goitre presenting with features of hyperthyroidism in the past three years: lid retraction, neurovegetative lability, weight loss and cardiac arrhythmia. After a prolonged preoperative equilibration, she underwent a difficult bilateral thyroidectomy, owing to friability and hemorrhage.

The inhomogeneous multinodular specimen weighted 110 grams and the paraffin section showed foci of papillary carcinoma with highly suggestive malignancy. (13)

The incidence of cancerous thyroid nodules in cases of hyperthyroidism (0.3-16.6%) is similar to the one described in general thyroid pathology, imposing in all such lesions an aggressive diagnostic approach to exclude malignancy. US guided FNAB is the best way to identify and define these lesions. Presence of suspected or confirmed carcinomas is decisive in choosing the indication and extent of surgery, often followed by completion operations, radioiodine and hormonal therapies, in concurrent lesions. (4,13)

Papillary thyroid carcinomas represent the most frequent type of TC. They include many variants, which however do not modify their most optimistic prognosis among glandular carcinomas. Outside the familial variant it presents tall and columnar subtypes, follicular and insular patterns, diffuse sclerosing or multicentric lesions, all with little impact in face of the general biological behaviour of these tumours. (3,15)

Follicular thyroid carcinoma accounts for about 15% of thyroid cancers and habitually presents as a slow-growing asymptomatic thyroid nodule which may extend into the opposite lobe and the adjacent cervical tissues or can metastasize to distant sites, but secondary lymph node involvements are rare. Microscopically it is usually compact, composed of small follicles, trabeculae and solid cellular masses. (4,15)

Hürthle cell carcinoma (HTC) is a relatively rare tumor in this group, generally defined as a lesion constituted of at least 75 per cent Hürthle cells (oncocytes). These large and poly-gonal shaped cellular elements are characterized by abundant acidophilic, granular cytoplasm due to numerous mitochondrial, large nuclei with prominent nucleoli, few or no lymphocytes and scanty or discrete colloid. The malignant forms of oncocytoomas present significantly larger size, vascular and/or capsular invasion together with lymph node spread, as in our unique observation. (15,16)

A 61-year-old female presented a rapidly growing tumor in the right thyroid lobe with huge N2 adenopathy, fixed to the underlying structures and measuring 8x6 cm. (Fig. 5) FNAB showed pleomorphic, overlapping clusters of Hürthle cells with significant nucleoli and background necrosis strongly suggesting the possibility of an oncocytooma. The patient underwent a near total thyroidectomy with right neck dissection. Paraffin section confirmed the diagnosis revealing vascular, capsular and lymph node invasion. She received radioiodine ablation therapy and survived more than five years. (Fig. 6)

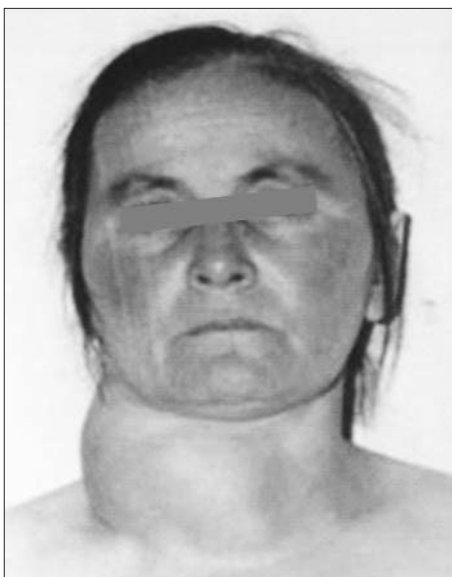


Figure 5. Hurthle cell carcinoma

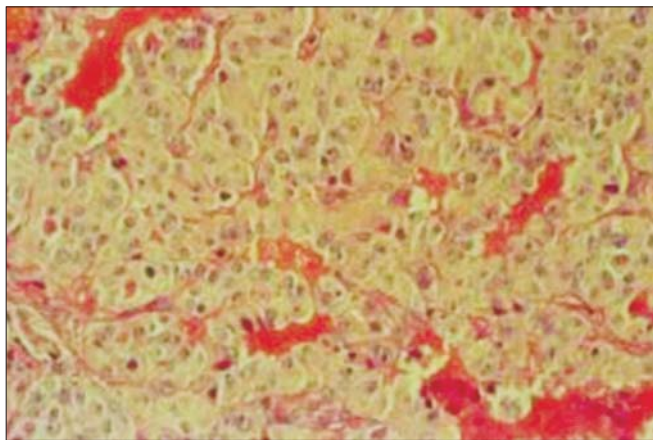


Figure 6. Same case: paraffin section

The most “inquisitive” tumor of the thyroid gland is medullary carcinoma (MTC) which realizes the unique form of infraclinical thyroid neoplasia sustained by C-cell hyperplasia, its assumed precursor. Physiologic (reactive) and neoplastic C cell hyperplasia (MTC in situ) followed by clearly definite medullary carcinoma is a yet unclear sequence comprising also the sporadic or hereditary forms of the tumor. Also, its associations with a lot of special conditions as MEN type II A and B, hyperparathyroidism and Hashimoto disease, and especially its foreboding signal marker calcitonin make MTC a predictable entity, but at the same time endowed with a considerably variable prognosis. (5,6,18) Our experience is reduced to only two advanced cases.

The most significant is a 59-year-old woman developing a refractory, persistent diarrhea for about three months, labelled as an irritable colon syndrome, but a fortuitous endocrinologic consult revealed a right thyroid swelling with enlarged cervical nodes. There was no family history of endocrine disorders. Thyroid ultrasound showed a hypoechogenic 6 cm mass, which

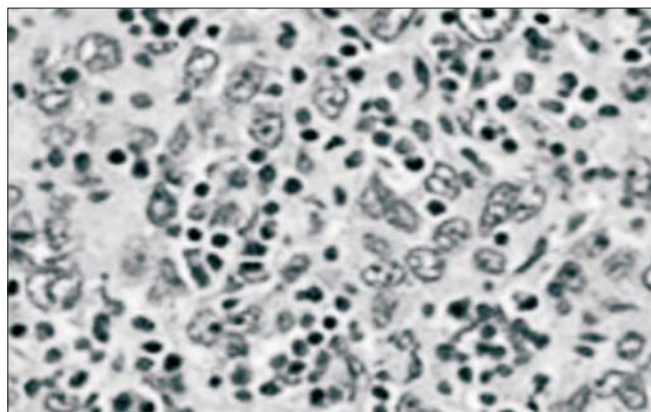


Figure 7. Medullary thyroid carcinoma

did not concentrate the radiotracer on the scintigraphy. FNAB revealed giant cells with enlarged nuclei and metachromatic cytoplasmic granules. Her serum level of thyroid hormones was normal, while calcitonin was 694 pg/ml and CEA 310 pg/ml. A total thyroidectomy with standardized neck dissection was performed, but the patient failed to attend the control visit. (Fig. 7)

The second confirmed case was considered inoperable from the beginning due to his age (67 years), associate pathology and presence of metastases.

A total thyroidectomy with meticulous removal of the central, lateral neck and upper mediastinum nodes correlates with the highest survival rate for patients with MTC. Systemic chemotherapy has shown only very limited efficacy. Treatment with radioactive iodine is ineffective since C-cells do not take up the isotope. The modern concept of “codon-directed” surgery supports prophylactic total thyroidectomy performed on the basis of positive genetic screening on young members of kindred with MEN 2A, before the development of the MTC. (18,19)

Located on an intermediate position between differentiated TC and potentially lethal anaplastic carcinoma, insular thyroid carcinoma (ITC) is actually integrated into the poorly differentiated TC types, together with trabecular and solid tumors being characterised by the presence of clusters (insulae) of small, uniform tumoral cells with vascular and capsular invasion, forming little follicles that secrete thyroglobulin. ITC has an accelerated evolution towards local and distant metastases. Ultrasound and FNAB are only descriptive, frozen section being the gold diagnosis standard. Radical surgery i.e. total thyroidectomy completed by lateral and central neck dissection succeeded by radioiodine therapy allowed a satisfactory survival. (3,5,20,21)

A 59-year-old man with huge apparent isolated laterocervical adenopathy without any clinical or imaging identifiable thyroid or other type of neck lesions is admitted in our unit. FNAB oriented the diagnosis towards a nodal metastasis of a follicular thyroid carcinoma. Intraoperatively completing the selective neck dissection, a solitary 5 mm centrolobar nodule is identified and a total thyroidectomy was performed. Pathology showed neoplastic cells arranged in nests

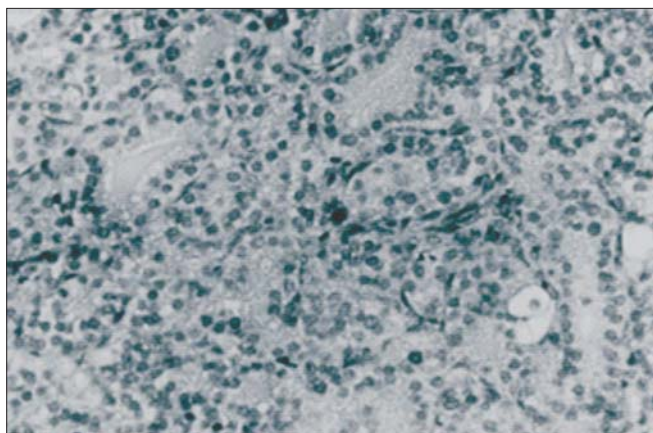


Figure 8. *Insular thyroid carcinoma*

separated by hyaline stroma, with grooved nuclei, rare mitosis and necrotic areas, all demonstrative for an ITC. (Fig. 2 and 8)

Radioiodine complementary therapy assured a stable cure at 24 months follow-up.

Anaplastic (undifferentiated) thyroid carcinoma (ATC) is the thyroid tumor with the highest malignancy level, rapidly invading contiguous structures and metastasizing throughout the body, and constitutes about 1-2% of all thyroid carcinomas. Our 12.5 per cent is due probably to the surrounding endemic area and the tertiary status of the unit. The usual clinical feature is an accelerate, sometimes painful enlargement of a long-standing goitre. The mass is hard in consistency, fixed, and invades the adjacent structures, with invasion of regional lymph nodes and distant metastases. Accompanying symptoms may include hoarseness, dysphonia, dysphagia, dyspnoea and local pain. A swift course caused the patient's death within few months after diagnosis. Upon microscopic examination the lesion is composed of multiple atypical cells which exhibit numerous mitoses and a variety of patterns: spindle-shaped, giant multinucleate and squamous cells. Areas of polymorphonuclear infiltration and necrosis are also present, together with PTC or FTC nests. (3,4,23)

The management of ATC varies between optimistic attempts, including surgical extensive resections completed by tenacious radiotherapy and chemotherapy with isolated prolonged survivals, and a sceptic attitude discouraging any radical but palliative surgery and recommending only chemoradiation treatment. The majority of statistics however offers a median survival period of only six months. (4,22,23) Reviewing our ten cases [4 men and 6 women with a median age of 66 (range 44-78) years) with pathologically confirmed diagnosis, local disease was present in all patients with nodal (7 cases) and distant (6 cases) metastases (mainly in the lung]. Approximately half of the patients had a history of preceding nodular goitre. The enormous tumor volume, important extrathyroid and nodal extensions, secondary deposits, age and poor general condition drastically restricted the surgery. Total thyroidectomies with neck dissection, which were possible only in two cases, along with two debulking exereses - one imposed by thacheostomy, and two biopsies after cervicotomies were all our endeavours, despite of which all the patients, although sub-

mitted to radiotherapy and chemotherapy, died after 2 weeks-6 months.

Metastases to the thyroid may occur with different incidence, the kidney, colon, lung and breast being the common sites of origin. The primary lesion may be unapparent, even cured many years ago. These secondary neoplastic deposits often showed up indistinguishable from a primitive malignant tumor or as an ordinary benign nodule. In 80 per cent of cases the clinical evidence of non-thyroid malignancy and its metastases in the thyroid were synchronous. Diagnosis is established by FNAB, but open biopsy or even surgery, together with other imaging studies and/or tumor markers must also be taken into consideration to clarify the real identity of these eventualities. Their outlook is poor, but in some favourable circumstances few individual patients can require different (even surgical) methods of treatment. (6,22)

Our only such case, a 51-year-old female was referred to us by the endocrinologist for a FNAB diagnosed thyroid carcinoma with a unique lung metastasis in view of a total thyroidectomy allowing ulterior radioiodine administration. After inadvertent surgery it was proven that the thyroid lesion was in fact secondary to a bronchopulmonary carcinoma.

Primary thyroid lymphomas (PTL) account for less than 5% of all thyroid malignancies and for approximately 2% of extranodal lymphomas. The most common histological type is non-Hodgkin's lymphoma, especially in its large-cell variant. The great majority of cases show evidence of chronic lymphocytic thyroiditis indicated by antithyroid antibodies and microscopy. Unfavourable prognostic factors are the advanced stage of the tumor, and bulking with perilesional tissue spread. PTL are susceptible to radiochemotherapy and long-term survival rates of more than 50% were reported in patients with localized disease. Whether total thyroidectomy can further improve patient outcome has not yet been proved. (4,22)

SM, a 42-year-old female presented a 2.5 cm, right, firm thyroid nodule, nonhomogeneous on ultrasound images. FNAB showed cellular smears of mixed follicular and Hurthle cells on a background of mature lymphocytes displaying some nuclear atypia and scanty cytoplasm, but no definite malignant elements. Intraoperatively, in addition to the known "trivial" nodule, small cervical lateral, central and delphian lymph nodes were evidenced and excised. Frozen section showed no evidence of malignant or even suspected cellular elements. An extended right lobectomy with lymph node excision was performed. Pathology specified a diagnosis of non-Hodgkin lymphoma and the patient was referred to chemotherapy. (Fig. 10)

Discussions and Conclusions

The study does not refer to the most frequent or even unique and seldom described TC, but to some types of uncommon lesions that underwent surgery in our unit, characterized by the complexity and particularities of the tissue cell elements, clinical and histological associations or sometimes by capricious behaviour. They encompass a handful of conspicuous thyroid tumors, published as isolated cases or in small series, the majority without control reports. (8,13,24) Among these are



Figure 9. Inoperable anaplastic

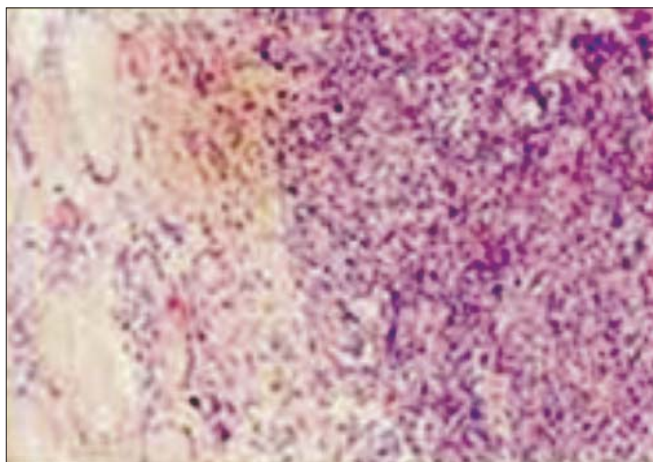


Figure 10. Non-Hodgkin thyroid lymphoma thyroid carcinoma

pediatric TC (two cases, of a 14 and a 15-year-old respectively appearing in the '90s with stable cure after total standard thyroidectomy), as well as 3 patients over 75 years, out of which only one with localised operable TC, and two with anaplastic lethal disease. To these "special" tumors we wish to add 22 reoperations for TC, among which two dedifferentiated lesions were discovered (progression from papillary to anaplastic carcinoma). (24)

Scanty literature mentioned also a few cases of thyroid sarcomas, carcinomas of vascular tissues, mucoepidermoid thyroid carcinomas, thyroid carcinoids, primary thyroid thymomas, malignant thyroid teratomas and so on. In all these cases the high and rapid tumoral growth and bad general condition similar to that of ATC grant succession and importance of the management resources. (3,5,22)

Of course surgery remains the mainstay therapy for most TC, especially in differentiated tumors, imposing the maximal feasible removal of tumor tissue, but with persisting controversy

with regard to the extent of glandular and lymph node resection. It is (seldom) completed by postoperative I-131 treatment, but systematic thyroid hormone replacement is required. The alternative option of minimally invasive, endoscopic or robotic thyroidectomy in cancers required appropriate patients selection. (4,25,26)

In some situations the dogma of the initial total thyroidectomy is not yet considered the primary option and debulking, airway clearing or hemostatic less than total resections can be regarded as a palliative resort. RAI therapy decreased both the recurrences and the death rates and is highly effective in advanced cases. Recent attempts with modulated reduced doses of radioiodine were successful. (4,5,26)

The continuous progress in understanding the molecular events occurring in thyroid carcinogenesis has led to the discovery of new targeted chemotherapy using drugs capable of selective inhibition of the pathways involved in mito- and angiogenesis signalling. Currently, two main gene alterations (i.e. BRAF and RAS mutations and RET/PTC rearrangements in follicular cell-derived TC) act as biomarkers predicting the prognosis of differentiated TC. Additional somatic and germline proto-oncogenes and particular oncogenes have been identified in MTC and ATC respectively. The latter are thought to be involved in the progression from differentiated to anaplastic histology. (23,26) Their identification together with a better understanding of thyroid carcinogenesis help develop innovative targeted therapies directed towards the most aggressive variants of TC, particularly in local advanced and metastatic iodine-resistant tumors. Recent proof evidenced that undifferentiated cellular elements are in fact TC stem cells constituting a driving force possessing an unlimited growth potential and resistance to conventional therapy regimen. They have been determined as "guilty" for TC invasiveness, dedifferentiation, metastases and recurrences. Other tumors typically respond to combined I-131 therapy (not always applicable), chemotherapy and/or radiotherapy (used as a palliative treatment for locally invasive TC), treatment cures instituted at times with promising effects. (27,28)

All these elements determined an increasing interest in alternative combination of therapeutic methods, including perfectible surgery with ideal-adapted regimen of RAI therapy and especially with new targeted chemotherapy. The ideal medical approach implies a multidisciplinary collaboration between researchers and practitioners.

Conflicts of interest

All authors declared there is no conflict of interest.

Authors contribution

M.R. Diaconescu performed the surgery and conceived the study. I. Costea and M. Glod members of the surgical team. M. Grigorovic expertise in pathology. S. Diaconescu drafted the study, monitored the childhood and Chernobyl patients, corresponding author.

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