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Diagnosis, pathology, and management of TSH-secreting pituitary tumors. A single-center retrospective study of 20 patients from 1981 to 2014
Diagnostic, pathologie et traitement des tumeurs thyroïdiques. Une étude monocentrique et rétrospective de 20 patients sur la période 1981-2014

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Abstract

TSH (thyroid-stimulating hormone)-secreting tumors are the rarest type of pituitary tumor. The objective of this study was to describe initial presentation and follow-up in patients presenting TSH-secreting tumors and to characterize the pathological features, based on a cohort of 20 patients treated in our referral center, between 1981 and 2014. Most of the patients (75%) were female, aged around 50 years (mean: 50 ± 13 years). Initial symptoms were hyperthyroidism (8/20) and/or tumor mass-related symptoms. Median time to diagnosis was 18 months. Biochemical hyperthyroidism was found in 15 patients. Most of the tumors were macroadenomas (75%) and 30% were invasive. Seventeen patients underwent transsphenoidal surgery. All tumors expressed TSH, with >50% positive cells. Eleven were monohormonal and 6 plurihormonal, expressing β TSH plus growth hormone (GH) and/or prolactin (PRL). Both subtypes showed high expression of Pit-1 and SSTR_{2A} somatostatin receptors. SSTR₅ was slightly expressed in the plurihormonal subtype. Ki-67 index was elevated ($\geq 3\%$) in only one tumor. Signs of hyperthyroidism were more frequent in the plurihormonal than in the monohormonal subtype. At final follow-up (median: 34.79 ± 66.7 months), 75% of the patients were in complete remission after surgery; persistent hyperthyroidism was controlled by somatostatin analogs, alone (n=3) or associated to radiotherapy (n=1). The multidisciplinary approach promoted early diagnosis and control of hyperthyroidism by neurosurgical treatment, associated to somatostatin analogs or not. Clinical/pathological correlations highlighted the variations in immune profiles and in clinical and biological symptoms.

Résumé

Les tumeurs thyroïdiques sont la forme la plus rare de tumeur hypophysaire. Cette étude a pour but de décrire la présentation initiale et les suites post-opératoires chez des patients présentant une tumeur thyroïdique ainsi que les caractéristiques pathologiques, dans une cohorte de 20 patients pris en charge dans notre centre de référence pendant la période de 1981 à 2014. La plupart des patients (75 %) étaient des femmes, âgées d'environ 50 ans (moyenne : 50 ± 13), présentant une hyperthyroïdie (8/20) et/ou des symptômes en lien avec la masse tumorale. Le délai diagnostique médian était de 18 mois. Quinze patients présentaient une hyperthyroïdie biochimique. La plupart des tumeurs étaient des microadénomes (75 %) ; 30 % étaient infiltrantes. Dix-sept patients ont bénéficié d'une chirurgie trans-sphénoïdale. Toutes les tumeurs exprimaient la TSH, avec un taux de cellules positives de > 50 %. Onze tumeurs étaient mono-hormonales et 6 étaient pluri-hormonales, exprimant la β TSH ainsi que l'hormone de croissance (GH) et/ou la prolactine (PRL). Les deux sous-types présentaient une expression élevée de Pit-1 et des récepteurs de somatostatines SSTR_{2A}. Le SSTR₅ était légèrement exprimé dans le sous-type pluri-hormonal. L'index Ki-67 n'était élevé ($\geq 3\%$) que dans une seule tumeur. Les signes d'hyperthyroïdie étaient plus fréquents dans le sous-type pluri-hormonal que dans le sous-type mono-hormonal. Au dernier recul (médiane : $34,79 \pm 66,7$ mois), 75 % des patients étaient en rémission totale après leur chirurgie. Toute hyperthyroïdie était contrôlée par les analogues de somatostatine, seuls (n = 3) ou associés à une radiothérapie (n = 1). La stratégie pluridisciplinaire favorisait un diagnostic précoce et le contrôle de l'hyperthyroïdie par la neurochirurgie, associée ou non aux analogues de somatostatine. Les corrélations clinico-pathologiques soulignaient la variabilité des profils immunitaires et des symptômes cliniques et biologiques.

Keywords: hyperthyroidism; Pit-1; pituitary tumor; somatostatin analogs; TSH-secreting tumor; TSH adenoma

Mots clés: hyperthyroïdie ; Pit-1 ; tumeur hypophysaire ; tumeur thyroïdienne ; adénome thyroïdienne

1.INTRODUCTION

Thyrotroph tumors or TSH-secreting pituitary neuroendocrine tumors (PitNET) [1] are the rarest pituitary tumors (0.5-3%), with a prevalence of one case per million [2]. Nevertheless, a study conducted in the Swedish population has shown an increased incidence and prevalence, over the last two decades, from one case/million to 2.8 cases/million [3]. The first case was described in 1960 [4] and the first pathological series of 9 cases in 1988 [5]. Since then several case series have been reported [3,6–13]. Transsphenoidal surgery is the treatment of choice, with biochemical remission achieved in 69.7% of cases according to a recent meta-analysis, and with higher gross total resection (GTR) obtained in microadenoma (87%) compared to 49% of cases of macroadenomas [14]. In some cases of persistent disease, medical treatment with somatostatin analogs (SSAs) can allow good control of symptoms [15] and also significant tumor shrinkage [8,11,15]. In the recent WHO classification, these tumors are classified as tumors of the Pit-1 family [16]. They are frequently plurihormonal [11,16,17] and express somatostatin receptors (SSTRs). The case of TSH-growth hormone (GH) tumors with acromegaly, hyperthyroidism [18] and the histological appearance of somatotroph tumors, represents a different subtype that is classified with the somatotroph tumors.

A recent literature-based review focused on the differential diagnosis, laboratory assessment, and the several steps that constitute the current diagnostic approach [19]. In this retrospective study, we present the evolution of the diagnostic approach and patient management in a cohort of 20 patients seen from 1981 to 2014 in our tertiary referral center. Clinicopathological correlations in 17 operated thyrotroph tumors highlighted the variability of the immunoprofiles, the clinical and biochemical expression of these tumors of the Pit-1 family and the good prognosis of these tumors, especially when they were diagnosed early.

2. PATIENTS AND METHODS

2.1. Patient population

We retrospectively reviewed the medical records of 20 patients diagnosed and treated for thyrotroph tumors, between October 1981 and July 2014, in the department of endocrinology in the Hospices Civils de Lyon, France, after obtaining approval from the local ethical committee. The patients were identified after a search in the pituitary registry (PITUI CARE-Lyon, registered with the French data protection agency CNIL, 16-021, and clinicaltrials.org, NCT02854228).

Collected data included patient demographics, medical history, clinical examinations, laboratory investigations, pituitary imaging, treatment modalities and pathology.

The diagnosis of thyrotroph tumor was based on the known criteria for such tumors [2,15,19]:

- 1) Typical signs and symptoms of hyperthyroidism and/or symptoms related to pituitary tumor mass,

- 2) Biochemical hyperthyroidism with non-suppressed TSH values,
- 3) Pituitary imaging showing a pituitary tumor. In the case of pituitary surgery, the detection of β TSH by immunohistochemistry confirmed the diagnosis of thyrotroph tumor.

2.2. Biochemical evaluation

Endocrine investigations were performed at each visit during the follow-up. TSH, free thyroxine (fT4) and free triiodothyronine (fT3) were measured using commercial immunometric assays. The values were considered as normal or elevated according to the reference values at the time of diagnosis since the reference values changed during the period studied (1981-2014).

The level of the alpha-subunit of pituitary glycoprotein hormones was measured in 12 out of the 20 patients, using a radioimmunometric assay (normal value in women $<1 \mu\text{g/L}$ in follicular phase and $<2.5 \mu\text{g/L}$ in postmenopausal period). The ratio between the alpha-subunit and TSH using the formula $(\alpha\text{-subunit } [\mu\text{g/l}]/\text{TSH } [\text{mUI/l}]) \times 10$ [15] was also evaluated in 11 cases.

Hyperprolactinemia was diagnosed in the presence of elevated plasma prolactin (PRL) levels $>25 \text{ ng/ml}$ according to our laboratory reference values.

2.3. Pituitary imaging studies

In almost all patients ($n=17/20$), a pituitary MRI was performed before and after intravenous gadolinium injection. For three patients, evaluated between 1981 and 1991, the initial assessment was done by contrast enhanced computer tomography. The maximum diameter of each tumor was measured in order to classify the tumors as

macroadenomas (maximum diameter ≥ 10 mm) or microadenomas (maximum diameter < 10 mm). The invasion in the cavernous and sphenoid sinuses was also evaluated according to Knosp's classification [20] with suprasellar extension not being considered as invasion.

2.4. Follow-up

Patients were considered as in complete remission when the biochemical profile showed normalization of thyroid function with no residual tumor on the post-operative pituitary MRI. Radiological follow-up was available for 15 patients. Recurrence was defined by the reappearance of thyroid profile disturbances consistent with thyrotroph tumor, after an initial complete remission.

2.5. Histological and immunohistochemical studies

The 17 tumor specimens obtained by transsphenoidal surgery were fixed in Bouin-Hollande (with copper) or zinc formalin fixative and embedded in paraffin. For routine histology, hematoxylin phloxine saffron (HPS) and Herlant's tetrachrome staining were performed. The diagnosis of thyrotroph tumor was based on automated immunohistochemistry (IHC) reactions performed with Benchmark XT, Ventana Medical Systems, Tucson, AZ, USA. The following antibodies and dilutions were used: monoclonal anti-PRL (1:400, Immunotech and Dako), polyclonal anti-GH (1:15000, NIADDK), polyclonal anti-adrenocorticotrophic hormone (ACTH) (1:1000, Dako), monoclonal anti-follicle stimulating hormone β subunit (FSH β) (1:6000, Immunotech), polyclonal anti-luteinizing hormone β subunit (LH β) (1:8000, NIADDK), monoclonal anti- β TSH (1:150,000 Immunotech) and polyclonal anti- β TSH (1:400, donation of B. Claustrat, Lyon), and

monoclonal anti- α -subunit (1:150, Immunotech). The level of expression of somatostatin receptors (SSTR_{2A}, SSTR₅) was studied in all the tumors and assigned a score from 0-12; a score >5 was considered as high expression according to Casar-Borota et al [21]. Pit-1 expression was also tested in 16/17 tumors and was non-interpretable in one. The proliferative rate (mitotic count and Ki-67 index) and expression of p53 were also studied as detailed previously [22]. The immunohistochemical reactions with the 4 last antibodies were performed on fresh sections of all tumors simultaneously. The references for the SSTRs antibodies and Pit1 antibody were the following: SSTR_{2A} (clone UMB-1, 1/4000, Abcam, Burlingame, California, USA), SSTR₅ (clone UMB-4, 1/500, Abcam, Burlingame, California, USA) (12) and Pit-1 (1/500, Novus Biologicals Europe, Abingdon, UK). The specificity of the Pit-1 antibody was tested on 10 FSH-LH-, 5 ACTH- and 5 PRL immunoreactive tumors. This antibody did not work on 6 tumors that were fixed in formalin-acetic acid-alcohol. All the tumors were independently reviewed by two pathologists (JT, AV), who were blinded to the clinical data. The prognostic five-tiered classification of the pituitary tumors based on invasion and proliferation was applied: grade 1a, non-invasive; 1b, non-invasive and proliferative; 2a, invasive; 2b, invasive and proliferative; and 3, metastatic [22].

3. STATISTICAL ANALYSIS

All descriptive quantitative data are reported as median values with a range or mean \pm standard deviation and the qualitative data reported as a percentage. The intergroup differences were assessed with the independent sample *t* test accepting $p < 0.05$ as statistically significant, and with the confidence interval set at 95%.

4. RESULTS

4.1. Latency to diagnosis and previous thyroid treatment

The latency to diagnosis from initial symptoms (Figure 1) varied from 3 to 133 months, with a median of 19 months. The median latency to diagnosis was 60 ± 42 months (10-133 months) before 2000 and then significantly reduced to 13 ± 18 months (3-60 months, $p=0.025$) after 2000. Before diagnosis of the thyrotroph tumor, five patients received antithyroid drugs (duration from 9 to 16 months) for normalization of thyroid function; another patient with hyperthyroidism and was positive for anti-thyroperoxidase and anti-TSH receptor antibodies, received antithyroid drugs and a dose of 11 mCi radioactive iodine that failed to normalize her thyroid function. One patient had a total thyroidectomy for papillary thyroid carcinoma stage pT1a.

4.2. Clinical symptoms of thyrotroph tumors

Table 1 presents the patient demographics, symptoms and treatment in the 20 patients of our cohort. The median age of the cohort was 50 ± 13 years (range 31-75 years) with a majority of females (75%).

The symptoms leading to the diagnosis of a thyrotroph tumor varied from one patient to another. At diagnosis, almost half of the patients ($n=8$; 40%) presented with symptoms of hyperthyroidism such as: palpitations/atrial fibrillation ($n=4$), cardiac failure ($n=1$), excessive sweating, fatigue, weight loss, severe osteoporosis ($n=1$) and exophthalmia ($n=2$). Six patients (30%) were diagnosed as having thyrotroph tumors found as a result of hormonal investigations for a goiter ($n=5$).

Eight patients (40%) initially presented symptoms of a pituitary tumor mass (chronic headaches (n=4), visual field defects (n=3)) and one patient presented with pituitary apoplexy and headache.

Six patients had menstrual disturbances among whom two presented with amenorrhea and galactorrhea leading to the diagnosis of hyperprolactinemia, hyperthyroidism and pituitary tumor.

4.3. Hormonal characteristics

Biochemical hyperthyroidism with non-suppressed TSH concentrations was found in 15/20 patients, with TSH values above the upper limit of normal (ULN) in 7 of them (46.6%), and fT4 levels above the upper limit of the normal range (ULN) in 11 of them (73.3%). All of the patients who were not operated had biochemical hyperthyroidism. For two patients, who presented clinical symptoms of hyperthyroidism (goiter and palpitations) with normal TSH values, the thyroid hormone levels were not evaluated. Out of the 17 patients operated on, initial biochemical evaluation was missing in 3 of them (noted as ND in Table 3). Two patients (2 and 10) with incomplete biochemical profile (normal TSH without available thyroid hormones), presented with clinical signs of hyperthyroidism (Table 3).

The level of alpha subunit was measured in 12 patients (median $4 \pm 4.85 \mu\text{g/l}$, range 1.2-16.9) and was above the ULN in 10 patients with a median of $3.95 \pm 4.88 \mu\text{g/l}$ (range 2.7-16.9 $\mu\text{g/l}$). Of these patients, six were postmenopausal women. The alpha subunit/TSH ratio was calculated in 11 patients and gave a median value of 11 (range 3.21-220).

Five patients presented with hyperprolactinemia with a median value of 47 ± 39.5 ng/ml (range 36-126 ng/ml). IGF1 levels were normal in all of the patients tested.

4.4. Pituitary MRI

Thyrotroph tumors were found to be macroadenomas in 75% of cases ($n=15$) with a median diameter of 13 ± 6.41 mm (range 10-26 mm), and microadenomas in 25% ($n=5$) with a median diameter of 5 ± 1.4 mm (range 5-8 mm). Ten thyrotroph tumors were diagnosed before 2000, nine of which were macroadenomas (mean diameter 12 mm) and one microadenoma. Ten thyrotroph tumors were diagnosed after 2000, six of which were macroadenomas (mean diameter 14.75 mm) and four microadenomas (Figure 1). We did not observe any differences in the tumor size of the macroadenomas diagnosed before and after 2000 ($p=0.46$). Six tumors (30%) were invasive, extending into the cavernous sinus in 20% of cases ($n=4$), into the sphenoid sinus in 5% ($n=1$) and both cavernous and sphenoid sinuses in 5% of cases ($n=1$).

4.5. Pathological characteristics

Seventeen patients (85%) underwent transsphenoidal surgery. All of the tumors exhibited the typical thyrotroph cytodifferentiation with large polygonal chromophobic cells with intertwined cytoplasmic processes, arranged in a diffuse pattern (Figure 2A). Perivascular fibrosis ($n=7$) and calcifications ($n=3$) were frequent (Figure 2B and C). By immunohistochemistry, all of the tumors were found to express β TSH (Figure 2D) and α -subunit. The percentage of positive cells varied from 20 to 100%, and in most tumors was greater than 60%. Almost all the tumors that were tested expressed high levels of Pit-1 (Figure 2F). Only one tumor had a Ki-67 index $\geq 3\%$. A mitotic count >2 was observed in

only one tumor. Expression of p53 was positive in seven tumors (41%). Ten tumors (58.8%) were low grade (grade 1a), 1 was graded 1b, six were invasive (35%, grade 2a) and none were invasive and proliferative (grade 2b).

Eleven tumors were monohormonal (65%) and six tumors plurihormonal (35%). Out of these 6 plurihormonal tumors (Tables 1 and 2), two co-expressed both TSH and GH (cases 16 and 17) while four co-expressed TSH and PRL (cases 12-15). All tumors were negative for FSH, LH and ACTH expression.

Clinically, there were no demographic differences (mean age and sex) between the group of patients with monohormonal and the group with plurihormonal tumors. Tumor mass-related symptoms were more frequent in the monohormonal group than in the plurihormonal group (7 vs 1).

Monohormonal tumors were larger than plurihormonal tumors (13.5mm vs 10mm, $p=0.03$) but clinical and biological signs of hyperthyroidism were consistent in the plurihormonal tumors (6/6) and more frequent than in the monohormonal subtype (5/11).

No significant differences between monohormonal and plurihormonal groups were found regarding tumor grade and invasion (4/11 vs 2/6).

The monohormonal (n=11) and plurihormonal TSH-PRL (n=4) tumors were characterized by polymorphous cells, fibrosis and calcifications and high expression of SSTR_{2A}, but no or a low level expression of SSTR₅. In contrast, the plurihormonal TSH-GH tumors expressed both SSTRs at high levels.

4.6. Follow-up and management

Figure 3 summarizes the management of the patients, based on a multidisciplinary approach. The median follow-up after diagnosis was 34.79 ± 66.7 months (2.47-192.11 months). Only three patients were treated exclusively with SSAs that led to an adequate control of the hyperthyroidism after the first 4 months of treatment.

In total, 17 patients underwent surgery (85%), 15 patients (75%) were naïve of any pre-surgical treatment with SSAs. Five patients were lost during follow-up after surgery. At the final evaluation (52.3 ± 74.97 months), 9 patients (75%), including the 2 microadenomas and 7 out of the 10 macroadenomas were in complete remission. The other 3 macroadenomas were controlled by SSAs (n=2) or required a combination of SSAs, ATDs and radiotherapy for control of the disease.

From the total of 10 patients operated for macroadenomas and with follow-up, 7 were in complete remission, 2 were controlled by SSAs, and one was controlled by SSAs, ATDs and RxT.

5. DISCUSSION

Thyrotroph tumors are the rarest pituitary tumor subtype with an incidence of 1.1% (4 out of 374 tumors) in our referral center between 2007-2012 [23]. The diagnosis of central hyperthyroidism represents a challenge due to easy misinterpretation of clinical presentation. The most frequent clinical symptoms are related to the presence of hyperthyroidism. According to two recent series, 89% to 92% of patients presented with symptoms of hyperthyroidism before being diagnosed as having a thyrotroph tumor [6,7]. In our cohort, the diagnosis of thyrotroph tumor was suspected based on the clinical symptoms of hyperthyroidism in only 40% of the patients, while it was associated

with a goiter in 62.5% of patient, a common finding in patients with thyrotroph tumors [6,12,15,18].

The diagnosis of a thyrotroph tumor based on biochemical hyperthyroidism with increased levels of thyroid hormones and non-suppressed TSH levels [2,15] was observed in 75% patients of our series. Biochemical euthyroidism is reported in up to 70% of patients [9,18,24,25]. The diagnosis remains difficult in some cases. A complete biochemical evaluation of thyroid function is required even in apparently nonfunctioning pituitary macroadenomas. In our cohort, 3 patients with histological diagnosis, had only biochemical hyperthyroidism. Due to its high variability in normal conditions, the measurement of the alpha-subunit of pituitary glycoprotein hormones may only very rarely help in the differential diagnosis from the syndrome of thyroid hormone resistance [2,19]. In the literature, unbalanced secretion of alpha-subunit and a ratio of alpha-subunit/TSH more than 1, has been found in 80% of patients with thyrotroph tumors [8,26]. In our series, 60% of patients had an increased alpha-subunit level and the alpha-subunit/TSH ratio had a median of 11. In contrast to the findings of a higher frequency of normal alpha-subunit levels among microadenomas reported by Socin et al [8], we observed no correlation between the diameter of the tumor and the alpha-subunit values.

The latency between the initial symptoms and the diagnosis of thyrotroph tumor decreased from 60 ± 42 months before 2000 to 13 ± 18 months after 2000. This can be explained by the introduction of ultrasensitive TSH assays and MRI that, since 2000, have allowed an earlier diagnosis. The analysis of the literature demonstrates that the latency to diagnosis in recent studies has tended towards a decrease from a median of 48

months to a median of 4.5 months [8,12]. These technical improvements have thus clearly allowed a better identification of thyrotroph tumors. Indeed, although rare, their incidence would appear to be increasing according to the Swedish national data [3] along with the increasing incidence of microadenomas [2,19] which is confirmed by the recent meta-analysis which shows that in papers published after 2000 the percentage of microadenomas diagnosed in surgical series increased to 22% from the figure of 11% reported before 2000. In our series thyrotroph tumors tended to be diagnosed more frequently in young patients, most often as macroadenomas before 2000, while since 2000 such tumors have also been diagnosed in older patients, with an increased incidence of microadenomas (Figure 1). Nevertheless, in our cohort macroadenomas still prevail (75%), as has been reported in other series [12,27] representing 79.6% of patients of the published cases [14]. Only 35% of the tumors were invasive, as has been previously reported (around 40%) [6,8] and 58.8% of tumors were low grade. Moreover, one study performing single-nucleotide polymorphism array analysis and whole exome sequencing in 8 tumors showed a low number of mutations, suggesting that thyrotroph tumors are not especially aggressive [28].

Our results indicated that there are two distinct groups of thyrotroph tumors, monohormonal and plurihormonal. The plurihormonal TSH tumors were defined by the typical thyrotroph cytodifferentiation and the co-expression of TSH and GH or PRL. Moreover, these tumors were all associated with clinical and biochemical signs of hyperthyroidism. They were different from the “plurihormonal poorly differentiated tumors of Pit-1 family” that are characterized by only patchy immunoreactive cells [29]. In the literature, the percentage of thyrotroph plurihormonal tumors reported is variable,

ranging from 0% to 100% (mean 50%) [19]. Indeed, the diagnosis of plurihormonality may be based on clinical, biochemical or immunohistochemical characteristics. Surprisingly, the symptoms of hyperthyroidism were more frequent in the patients with plurihormonal tumors as compared to the patients with monohormonal tumours. We found no correlation between hyperprolactinemia and tumoral secretion of PRL. We can thus hypothesize that the hyperprolactinemia was related to the pituitary stalk compression by large tumors. Immunohistochemical studies have demonstrated that thyrotroph tumors express a variable number of SSTRs [13,30]. In our series, all the thyrotroph tumors expressed a high level of SSTR_{2A}, while only 1 plurihormonal (TSH-GH) tumor expressed a high level (≥ 5) of SSTR₅.

The first line therapy for thyrotroph tumors is transsphenoidal surgery, which while allowing complete resection of the tumor in the majority of patients, has a reduced cure rate of about 60% in cases of pituitary macroadenomas with sinus invasion [2]. In our study, of the 17 patients who underwent pituitary surgery, after excluding those lost during follow-up ($n=5$), complete remission was achieved in 75% of the patients. This rate is similar to that reported by Yamada et al [6] and Onnestam et al [3] and higher than that reported in other studies [7,26]. The high remission rates have been explained mainly by small and non-invasive tumours.

An adjuvant pharmacological treatment (SSAs, dopamine agonists, radiotherapy) was necessary to obtain disease control in 25% of the patients of our series similar to the case for patients in the series reported by Onnestam [3], and compared to 78.6% and 57% in other studies [7,26]. Five patients were treated with SSAs after the diagnosis of a thyrotroph tumor. This treatment alone allowed good control of the disease in three

patients who were not operated. Of the other two patients, one had surgery because of a lack of control of the disease and the other had normalization of the thyroid hormonal profile but developed side effects. We observed no complete remission of thyrotroph tumors after pharmacological treatment with SSAs, in contrast to what has been previously reported in one patient [31].

According to the literature, the recurrence rate after surgery varies from 0 to 31% [6,8,11,25,32,33]. The results are conflicting because of the differences between studies in the criteria used to define remission, with for example some considering recurrence only in the case of hyperthyroidism, irrespective of the presence of a lesion shown on the pituitary MRI. In our series, we observed no recurrence, at four years post-surgery, despite the tumors being frequently large and fibrous. Only 35% were invasive (6/17), 58.8% were of low grade (grade 1a 10/17) and none of the tumors were grade 2b which is associated with bad prognosis [17,22].

In conclusion, over the last two decades, the introduction of ultrasensitive assays and improved imaging methods has allowed an earlier diagnosis of thyrotroph tumors. However, the diagnosis remains difficult and requires a complete biochemical evaluation. Pituitary surgery should be the first line therapy. The vast majority of the patients treated showed no recurrence, which was especially true for those patients with microadenomas. Clinicopathological correlations have highlighted the variability of the immunoprofiles, the frequency of the plurihormonal subtype and the high expression of SSTR₂ and Pit-1.

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Figure 1. The latency to diagnosis of thyrotroph tumors, according to the date of diagnosis and the tumor size.

Figure 2. Pathological characteristics of monohormonal and plurihormonal thyrotroph tumors

A- Morphological features of a thyrotroph tumor: Chromophobic cells showing slight nuclear pleomorphism. A few nuclei harbor prominent eosinophilic nucleoli (Haematoxylin Phloxine Saffron staining, original magnification x 400).

B- Perivascular fibrosis in a plurihormonal (TSH-GH) thyrotroph tumor (β TSH immunoreactivity, original magnification x 200).

C- Microcalcification in a plurihormonal (TSH-GH-PRL) thyrotroph tumor (Haematoxylin Phloxine Saffron staining, original magnification x 400).

D- Cytoplasmic β TSH immunoreactivity in a monohormonal thyrotroph tumor. Notice polygonal cells with marginalisation of the β TSH immunoreactivity. Original magnification x 400.

E- High membranous immunopositivity of SSTR2 in all the cells (score: 12) of a thyrotroph tumor. Original magnification x 200.

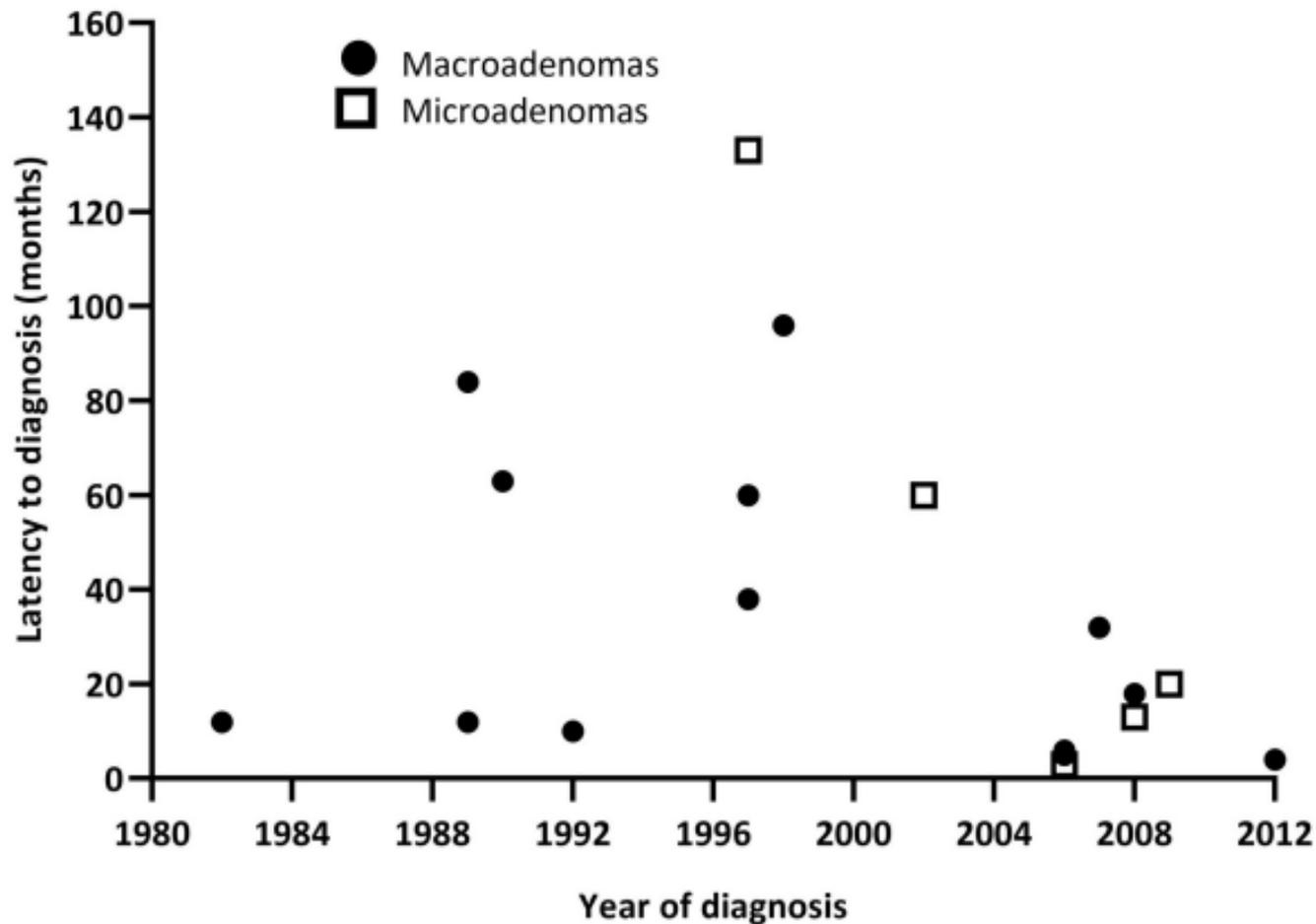
F- Pit-1 diffuse nuclear immunopositivity in a thyrotroph tumor. Original magnification x 200.

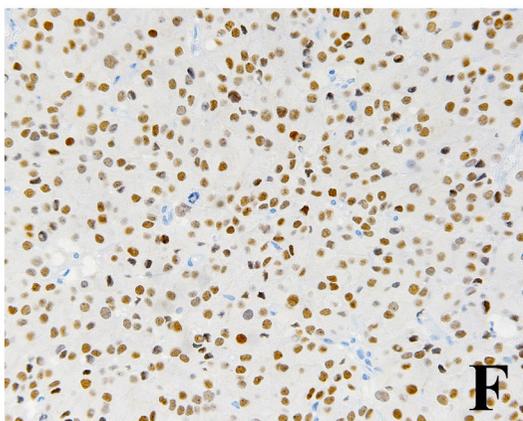
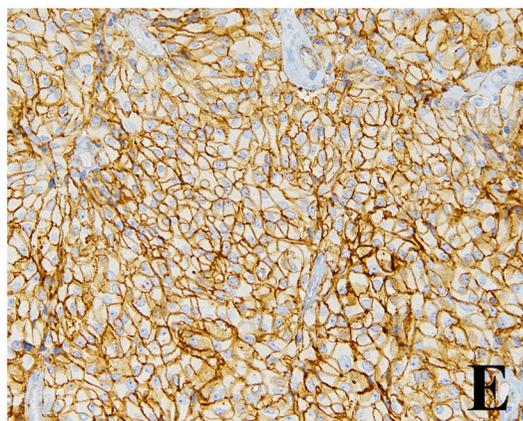
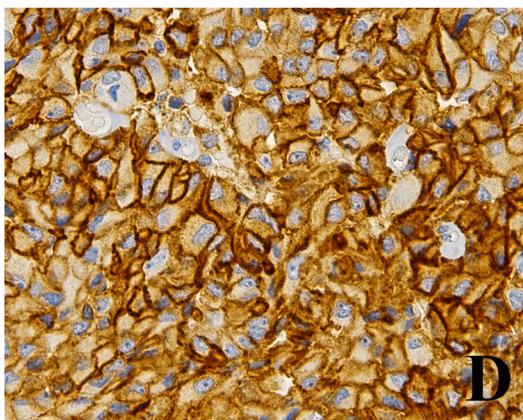
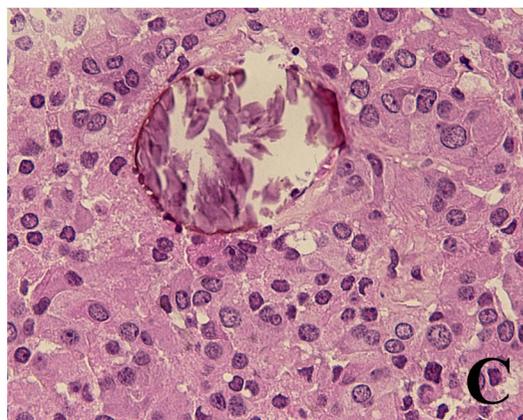
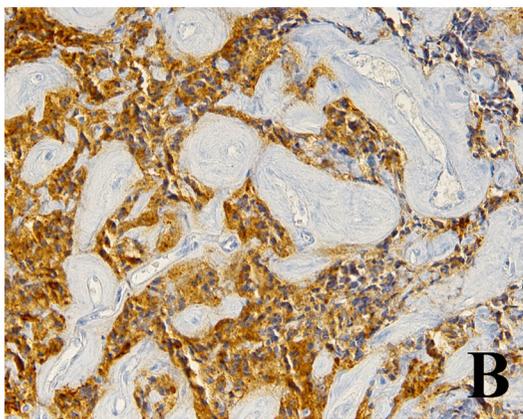
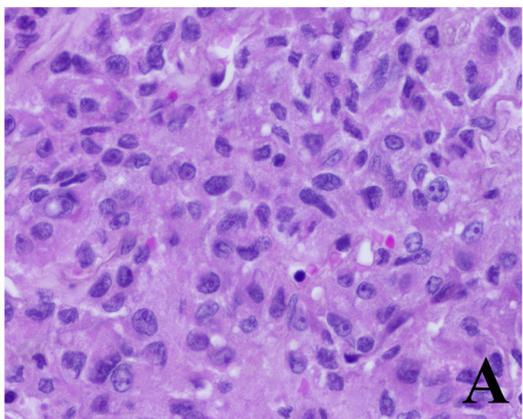
Figure 3. The management of the cohort of 20 patients with thyrotroph tumors

Table 1. Clinical signs and treatment of 20 patients with thyrotroph tumors

Table 2. Pathological characteristics of 17 thyrotroph tumors. Comparison between monohormonal and plurihormonal subtypes

Table 3. Clinicopathological correlations in 17 thyrotroph tumors





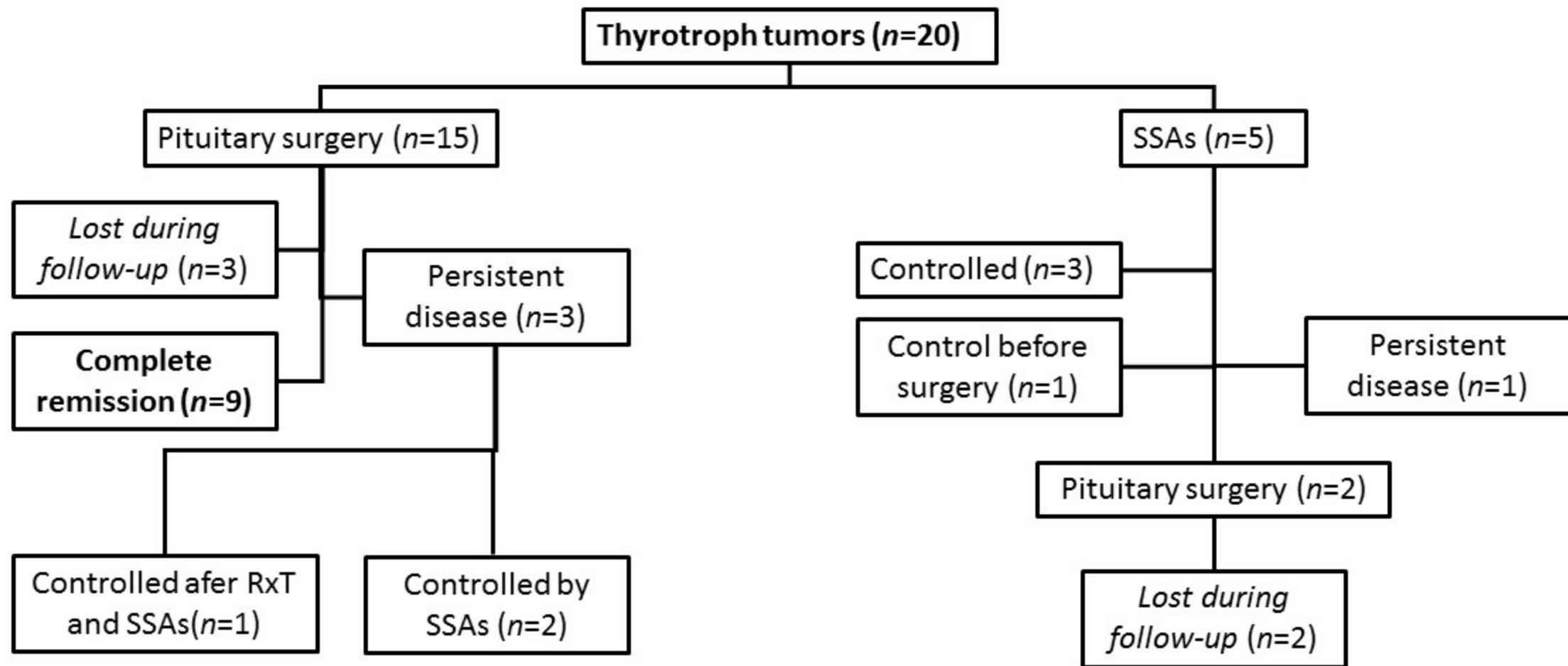


Table 1. Clinical signs and treatment of 20 patients with thyrotroph tumors

| Clinical signs N (%) | Total cohort | Patients operated | Monohormonal tumors | Plurihormonal TSH tumors |
|---------------------------------|---------------------|------------------------------|--------------------------------|-------------------------------------|
| Number of patients | 20 | 17 | 11 | 6 |
| Median age (years) | 50±13 (31-75) | 48±13 (31-74) | 47±14.6 (31-74) | 48±9.7 (39-63) |
| Sex | | | | |
| Female | 15 (75) | 12 | 8 | 4 |
| Male | 5 (25) | 5 | 3 | 2 |
| Signs of hyperthyroidism | 8 (40) | 8 | 2 | 6 |
| Cardiac symptoms | 4 | 3 | 1 | 2 |
| Weight loss | 1 | 0 | 0 | 0 |
| Tremors, asthenia | 3 | 2 | 0 | 2 |
| Goiter | 5 | 3 | 1 | 2 |
| Exophthalmia | 2 | 0 | 0 | 0 |
| Tumor mass symptoms | 8 (40) | 8 | 7 | 1 |
| Headaches | 5 | 5 | 4 | 1 |
| Visual disturbances | 3 | 3 | 3 | 0 |
| Thyroidectomy/ RAI | 2 (10) | 1 | 0 | 1 |
| Medical treatment | | | | |
| ATDs | 5 (23.8) | 4 | 1 | 3 |
| SSA | 3 (14.3) | 2 | 1 | 1 |
| Post-operative remission | 9 | 9 | 3 | 6 |

Abbreviations: ATDs: anti-thyroid drugs; RAI: radioactive iodine; SSA: somatostatin analogs

Table 2. Pathological characteristics of 17 thyrotroph tumors. Comparison between monohormonal and plurihormonal subtypes

| Pathological characteristics N (%) | Monohormonal Thyrotroph tumors | Plurihormonal Thyrotroph tumors |
|--|---|--|
| Number of tumors | 11 (65) | 6 (35) |
| Microadenoma | 1 | 2 |
| Macroadenoma | 10 | 4 |
| Median diameter (mm) | 13.5±7.7 (5-26) | 10±3.7 (5-16) |
| Invasion | 4 (36.36%) | 2 (33.3) |
| Immunohistochemistry | | |
| TSH | 11 | - |
| TSH-PRL | - | 4 |
| TSH-GH | - | 2 |
| SSTR ₂ ^a Expression (score>5) | 11 (100) | 6 (100) |
| SSTR ₅ Expression (score 1-9) | 0 | 4 (66) |
| Pit-1 (>80%) ^b | 9 | 3 |
| Mitoses n>2 | 1 | 0 |
| Ki-67 index | | |
| <3% | 11 | 5 |
| ≥3 % | 0 | 1 |
| p53 positive | 3 | 4 |
| Grades^c | | |
| 1a | 7 | 3 |
| 1b | 0 | 1 |
| 2a | 4 | 2 |
| 2b | 0 | 0 |

^a SSTR: somatostatin receptors; ^b non-interpretable for one tumor because of the tissue fixation and non-determined in one tumor; ^c according to J. Trouillas et al[20]

Table 3. Clinicopathological correlations in 17 thyrotroph tumors

| N° | Immunohistochemical characteristics | | | | | | | | Tumor characteristics | | | | | Clinical hyperthyroidism | Biochemical hyperthyroidism | |
|----|-------------------------------------|-------|-------|-------|-------|-----------------|------|------|-----------------------|----------|-------|--------|--------------------------|--------------------------|-----------------------------|-----------------------|
| | TSH | SSTR2 | | SSTR5 | | PIT 1 | PRL | GH | Type | Invasion | Ki-67 | Grades | Various | | | Maximum diameter (mm) |
| | % | % | score | % | score | % | % | % | | | % | | | | | |
| 1 | 40-60 | 100 | 12 | 20 | 1 | 100 | 0 | 0 | TSH | 0 | 0.5 | 1a | fibrosis | 10 | 0 | ND ^a |
| 2 | 20 | 100 | 12 | 80 | 3 | 80 | 0 | 0 | TSH | 0 | 0 | 1a | fibrosis | 12 | 1 | 1 |
| 3 | 80 | 100 | 12 | 0 | 0 | 0 | 0 | 0 | TSH | 1 | 0 | 2a | fibrosis, calcifications | 21 | 1 | 1 |
| 4 | 100 | 100 | 12 | 0 | 0 | 80 | 0 | 0 | TSH | 0 | 0 | 1a | | 25 | 0 | ND |
| 5 | 100 | 100 | 12 | 100 | 4 | 80 | 0 | 0 | TSH | 1 | 0 | 2a | | 25 | 0 | ND |
| 6 | 0-80 | 10-80 | 2-12 | 0 | 0 | 0 | 0 | 0 | TSH | 0 | 0 | 1a | calcifications | 10 | 0 | 1 |
| 7 | 95 | 100 | 12 | 0 | 0 | 100 | 0 | 0 | TSH | 1 | 1.5 | 2a | | 26 | 1 | 1 |
| 8 | 100 | 100 | 12 | 0 | 0 | 80 | 0 | 0 | TSH | 0 | 0 | 1a | | 5 | 1 | 1 |
| 9 | 70 | 80 | 9 | 50 | 2 | 80 | 0 | 0 | TSH | 0 | 0 | 1a | | 13.5 | 0 | 1 |
| 10 | 80 | 100 | 12 | 10 | 1 | 100 | 0 | 0 | TSH | 1 | 0 | 2a | fibrosis | 25 | 1 | 1 |
| 11 | 80 | 100 | 12 | 5 | 1 | 80 | 0 | 0 | TSH | 0 | 0 | 1a | | 12 | 0 | 1 |
| 12 | 80 | 80 | 9 | 5 | 1 | 80 | 5 | 0 | TSH-PRL | 1 | 0 | 2a | fibrosis | 8 | 1 | 1 |
| 13 | 20-50 | 100 | 12 | 0 | 0 | 100 | 5-80 | 0 | TSH-PRL | 1 | 0.5 | 2a | fibrosis, calcifications | 10 | 1 | 1 |
| 14 | 100 | 80 | 9 | 0 | 0 | NI ^b | 100 | 0 | TSH-PRL | 0 | 0 | 1a | | 5 | 1 | 1 |
| 15 | 80 | 80 | 6 | 20 | 1 | ND | 100 | 0 | TSH-PRL | 0 | 2 | 1a | | 12 | 1 | 1 |
| 16 | 80 | 100 | 12 | 80 | 3 | 0 | 0 | 80 | TSH-GH | 0 | 0 | 1a | fibrosis | 10 | 1 | 1 |
| 17 | 80 | 100 | 12 | 80 | 9 | 100 | 0 | 0-60 | TSH-GH | 0 | 3.7 | 1b | | 16 | 1 | 1 |

Absent=0; Present=1; Abbreviations: ^a ND: non determined; ^b NI: non interpretable