INVITED REVIEW

Aggressive corticotroph tumors and carcinomas

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1 | INTRODUCTION

Corticotroph tumors represent 4%–8% of all clinically secreting pituitary tumor types. Most of these are microadenomas, responsible for cortisol excess that may be cured after trans-sphenoidal surgery; however, about 10% of secreting corticotroph tumors are macroadenomas associated with a poor surgical prognosis.1 Including silent corticotroph adenomas, defined as pituitary tumors without clinical evidence of Cushing’s disease, corticotroph tumors overall represent up to 15% of all pituitary neuroendocrine tumors (Pit-NETs).2

Aggressive pituitary tumors (APT) are defined as invasive tumors which present with multiple recurrence and do not respond to standard therapies (standard medical treatments such as dopamine agonists and somatostatin analogs, surgery and radiotherapy).3 These tumors lead to increased morbidity and mortality, and are suspected in the case of unusually rapid or symptomatic tumor growth, despite appropriated treatments including surgery. Pituitary carcinoma (PC) is defined when distant metastases are identified, and is associated with poor survival (median survival <4 years after diagnosis of distant metastasis).4 The epidemiology of this rare entity is not well-described; aggressive pituitary tumors seem to represent <2% of macroadenomas, while pituitary carcinomas represent <0.1% of pituitary tumors. Despite the rarity of this clinical situation, all published studies confirm that corticotrophic adenomas are overrepresented in APT and PC, representing 30%–50% of aggressive pituitary tumors or pituitary carcinomas.5,6

This review, which forms part of a special issue on “Update of Cushing’s Syndrome: 100 years after Minnie G”, will focus on the clinical, pathological and molecular characteristics of aggressive corticotroph tumors and carcinomas, and to describe the results obtained with currently available treatments.

KEYWORDS
aggressive pituitary tumor, corticotroph tumor, Cushing’s disease, pituitary carcinoma, temozolomide

Abstract
Pituitary tumors are generally benign, although in rare cases aggressive pituitary tumors (APTs) and carcinomas present important diagnostic and therapeutic challenges and are associated with a high mortality rate. Almost half of these APTs and carcinomas are corticotroph tumors, suggesting a specific prognosis. Clinical, pathological and molecular prognostic markers are limited and do not allow early management of these tumors. Temozolomide remains the first-line treatment once a diagnosis of aggressive pituitary tumor or carcinoma has been made. Novel alternative treatments exist, including immune checkpoint inhibitors, which can be used in the case of temozolomide treatment failure. The aim of this review is to present the clinical, pathological and molecular characteristics of aggressive corticotroph tumors and carcinomas, and to describe the results obtained with currently available treatments.
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2 | CLINICAL CHARACTERISTICS

A recent review of the literature revealed that corticotroph carcinomas represent 34.7% of all published pituitary carcinomas. Most of these cases were case reports; however, recent evaluation of temozolomide efficacy to treat these tumors permits the description of numerous cases. At initial diagnosis, no clinical marker can predict the occurrence of metastasis during follow-up; however, progression from microadenoma to carcinoma is extremely rare. The time from diagnosis to presentation with aggressive behavior, or occurrence of metastasis, is highly variable being from months to years. The diagnosis of a carcinoma usually occurs in the fourth decade and, contrary to what is seen in benign corticotroph tumors, there is no male or female preponderance, suggesting that macrocorticotroph tumors in male may be associated with poor prognosis. The proportion of silent corticotroph adenomas also seems higher than expected, but more importantly the change from initially silent to functional corticotroph tumor seems to be the main prognostic marker that is predictive of malignancy. In such a situation, or in patients with aggressive pituitary tumors and either site-specific symptoms suggestive of secondary localizations (i.e., back pain, neurological complaints etc.) or discordant biochemical and radiological findings, the European Society of Endocrinology (ESE) guidelines recommend performing an extension assessment to look for metastatic disease. Most secondary tumor localizations are intracranial or spinal, but liver, cervical lymph nodes and bone, and in rare cases, lung, endolymphatic sac, or orbit can be affected.

The impact of bilateral adrenalectomy (BADX) on corticotroph tumor progression has been recently reviewed and its implication on corticotroph tumor behavior is uncertain. Indeed, patients with aggressive corticotroph tumors are more prone to undergo BADX and no study has thus far confirmed that loss of feedback inhibition accelerates tumor growth or induces metastasis. These tumors might be either particularly sensitive to loss of feedback inhibition after BADX or may exhibit a distinct intrinsic aggressiveness. In summary, clinical markers in the case of these tumors are limited and should be combined with histopathological or molecular markers.

3 | HISTOPATHOLOGY OF CORTICOTROPH AGGRESSIVE TUMORS AND CARCINOMAS

The 2017 World Health Organization (WHO) classification defines corticotroph tumors as neoplasms derived from the T-PIT-driven cell lineage. The T-PIT (encoded by TBX19 or T-Box transcription factor 19 gene) is a critical transcription factor involved in the differentiation of corticotroph cells. Its interaction with other cofactors, such as NeuroD1, is required to activate the pro-opiomelanocortin (POMC) gene. The detection of T-PIT by immunohistochemistry is now available and can be used in challenging cases, especially in hormone-immunonegative tumors. The prototypical example of a corticotroph tumor is the microadenoma that causes Cushing's disease. Histologically, this T-PIT-positive tumor is composed of granular basophilic cells showing diffuse cytoplasmic expression of low-molecular-weight cytokeratins (LMWCKs) and ACTH. These tumors usually express the somatostatin receptor (SSTR5) which is a target of pasireotide, a somatostatin analog. Corticotroph APTs and carcinomas may also show the same histopathological features (Figures 1A–C and 3A,B).

As for other Pit-NETs, the development of metastases is required to qualify a corticotroph tumor as a “carcinoma”. Identifying corticotroph tumors that may follow an aggressive course solely using histopathology is challenging and controversial. No single histopathological characteristic can accurately predict a malignant or aggressive course. Currently, the use of multiple clinical and pathological parameters is a means to identify those tumors that have a high risk of an unfavorable course.

In pituitary carcinomas overall, the mitotic count is usually greater than 2 per 10 high-power fields and the median Ki67 proliferation index 10% (Figure 1D). P53 immunopositivity is typically more prevalent in pituitary carcinomas and does not significantly differ from what is seen in APTs (Figure 1E). In corticotroph carcinomas, mitotic activity and Ki67 proliferation index are typically higher in the metastatic lesion than in the primary tumor. P53 immunoreactivity also follows this trend. These observations have led to the proposal that pituitary tumors with increased mitotic activity, elevated Ki67 proliferation index (>3%), and diffuse P53 immunoreactivity should be termed “atypical adenomas” in earlier WHO classifications. However, this definition was not precise enough to allow for easy and reproducible use, and no clear clinicopathological correlation emerged from this concept. Consequently, the term “atypical adenoma” was abandoned in the last WHO classification in 2017.

Some authors have developed a “mixed” clinicopathological classification to overcome these difficulties. In the French five-tiered classification, two criteria are considered: invasiveness assessed by MRI and peroperative surgical observation (1: noninvasive/2: invasive) and proliferation assessed by microscopy (a: nonproliferative/b: proliferative). Proliferation markers used include mitotic count, Ki67 proliferation index, and P53 immunostaining. Several studies have shown that this classification appears to be an interesting tool for identify pituitary tumors with a higher risk of recurrence/progression.

Consequently, the ESE guidelines recommend the analysis of Ki67 proliferation index in all pituitary tumors and mitotic count and P53 immunostaining should be assessed in tumors harboring a Ki67 index >3%.

The 2017 WHO classification recognizes that some types of pituitary tumors may show a more aggressive course. Among corticotroph tumors, silent corticotroph adenomas and Crooke cell adenomas are considered as “high-risk” adenomas.

3.1 | Silent corticotroph adenoma

Silent corticotroph pituitary adenomas (SCAs) are either densely granulated (silent subtype 1) or sparsely granulated (silent subtype 2)
corticotroph tumors with no clinical or biochemical features of Cushing’s disease.\textsuperscript{21,22} Histologically, the typical appearance of SCA includes a pseudopapillary architecture, sparsely granulated neoplastic cells (Figure 2A), cytoplasmic expression of LMWCKs, and variable expression of ACTH. Some authors have associated SCA with a poorer prognosis and the 2017 WHO classification classifies these tumors as a subtype of “high-risk” adenoma.\textsuperscript{11,23} However, in one meta-analysis of 297 patients, the risk of recurrence of SCA was not significantly higher than that of other functioning pituitary adenomas.\textsuperscript{24} Interestingly, these tumors are characterized by mixed corticotroph and gonadotroph transcriptomic signatures.\textsuperscript{25} The gonadotroph nature of these tumors is demonstrated by the expression of GATA3 together with the corticotroph lineage specific transcription factor TPIT\textsuperscript{25} (Figure 2B,C).

3.2 | Crooke cell adenoma

Crooke cell adenoma is a very rare subtype of corticotroph tumor. In this tumor, more than 60% of neoplastic cells harbor a ring-like cytoplasmic accumulation of hyaline material (Figure 2D).\textsuperscript{26} This material corresponds to LMWCKs and is typically found in normal corticotroph cells of patients with hypercortisolism (the so-called “Crooke cells”) (Figure 2E).\textsuperscript{27} Crooke cell adenomas are generally macroadenomas associated with Cushing’s disease. In comparison to classical macroadenomas with Cushing’s disease, they show a higher rate of cavernous sinus invasion but no statistically significant difference regarding the rate of recurrence.\textsuperscript{27} Their aggressiveness is thus debatable. Immunopositivity of MGMT in Crooke cell adenomas is mostly weak, in contrast to that seen in classical corticotroph adenomas.\textsuperscript{28}

Corticotroph tumor progression after bilateral adrenalectomy, known as “Nelson’s syndrome”, has a mean prevalence of 43%\textsuperscript{10} and is often considered as a severe complication of adrenal surgery in patients with Cushing’s disease. In one published study, the pathological characteristics, including mitotic count and Ki67 immunolabelling, were not found to be predictive of tumor progression.\textsuperscript{29}

4 | MOLECULAR PROGNOSTIC FACTORS

A better understanding of the genetic and molecular factors that influence tumor behavior would help clinicians adapt treatment and follow-up Pit-NETs identified as being at risk of aggressiveness. To date there is no strong factor that explains, or is predictive of corticotroph tumor behavior.
Recent studies have demonstrated that molecular alterations in Pit-NETs are closely associated with the tumor type. As corticotroph tumors represent the first aggressive Pit-NETs and present a higher rate of somatic mutations than other types, they are a particular area of interest. Aggressive corticotroph Pit-NETs are rare and generally develop many years after a Pit-NET diagnosis, so identification of a strong predictive factor using high power studies are not feasible. Nevertheless, some genetic alterations raise concern, as these have been preferentially found in invasive, large or recurrent tumors, and should thus be further explored.

The most common somatic mutations found in corticotroph Pit-NETs are $USP8$-activating mutations, first described in 2014. $USP8$ encodes a deubiquitinating enzyme that impairs EGFR degradation and induces activation of the EGFR pathway and then POMC transcription. $USP8$ mutations are found in around 40% of Cushing’s disease cases and are associated mainly with small and highly secreting tumors. Some studies have reported higher post-surgical remission of these tumors but an increased risk of recurrence. $USP8$ mutations have also been exceptionally described in a pituitary carcinoma and do not appear to be associated with aggressive behavior.

$USP48$ activating mutations have been described in 10%–20% of corticotroph Pit-NETs and these lead to activation of the Hedgehog signaling pathway via deubiquitination of Gli1. They appear to be associated with smaller tumor size but a recent study of 46 tumors reported 50% rate of invasion in tumors carrying $USP48$ mutations versus 4% in wild-type tumors.

Some somatic mutations in $NR3C1$, which encodes the glucocorticoid receptor, have been reported in around 6% of secreting corticotroph tumors. These mutations may reduce glucocorticoid receptor expression, its ability to suppress POMC and ACTH secretion, and induce increased proliferation. An association with aggressiveness was suspected, since it had already been described once in a Nelson syndrome patient who required an emergency craniotomy despite two trans-sphenoidal surgeries and one radiation treatment, but the association was never confirmed.

A role for impaired expression of $CABLES1$ in the development of corticotroph tumors has also recently been described. This cell cycle regulator is activated by glucocorticoids in corticotroph cells and its impaired expression has been described in corticotroph tumors. In a recent cohort study, germline missense mutations were found in 2/146 children and somatic missense mutations in 2/35 young adults screened. All were $USP8$ wild-type, had large and proliferative tumors, three required a second surgery and one required radiotherapy, so this rare mutation may be associated with a more aggressive pattern.

On rare occasions $BRAF$ mutations have been described in corticotroph Pit-NETs, inducing an activation of ERK signaling. One study reported $BRAF$ mutations in 16% of Cushing’s disease subjects.

**FIGURE 2** Histotypes of corticotroph aggressive tumors. (A) Silent corticotroph tumors are typically composed of regular cells with chromophobic or slightly basophilic cytoplasm (hematoxylin, phloxine, saffron [HPS] staining, original magnification [OM] × 200). (B) Silent corticotroph tumors express the T-PIT transcription factor as do all other tumors of the corticotroph lineage (T-PIT immunohistochemistry, OM × 100). (C) Some silent corticotroph tumors show immunoreactivity for GATA3, a transcription factor also expressed in gonadotroph tumors (GATA3 immunohistochemistry, OM × 100). (D) Crooke cell adenoma is composed of neoplastic cells harboring the ring-like hyaline change typical of normal corticotroph cells of patients with hypercortisolism (HPS staining, OM × 200). (E) The ring-like hyaline material corresponds to an accumulation of low-molecular-weight cytokeratins (cytokeratin 18 immunohistochemistry, OM × 200). (F) Expression of ACTH in Crooke cell adenomas is typically restricted to the paranuclear and peripheral regions of the cytoplasm (ACTH immunohistochemistry, OM × 200).
however this high proportion was not later confirmed and the impact on prognosis is unknown.

Recently, mutations in the tumor suppressor gene PTEN, which induces AKT/PI3K pathway upregulation, was found in a liver metastasis of an ACTH-secreting carcinoma, and had been previously described in a single case of ACTH carcinoma. Chromosomal alterations and copy number variations (CNV) are quite frequently found in Pit-NETs, especially in corticotroph tumors. Corticotroph tumors present a wide range in the quantity of CNVs, from no alteration to almost the entire genome being altered. The quantity of chromosomal alterations was reported to be associated with invasion in a cohort of 27 pediatric Cushing’s disease subjects, and with macroadenomas, silent or Crooke’s cell tumors, in another recent study on 22 patients. In our study on 33 corticotropic tumors, a higher level of CNVs seemed to be associated with macroadenomas, without reaching statistical significance, but was not associated with invasion, with silent tumors, nor with USP8 mutations. Overall, we also failed to find an association between tumor recurrence at 5 years and the quantity of CNVs.

In rare cases, corticotroph tumors can occur as a familial form. Germ-line mutations of MEN1 and AIP mainly result in PIT-1-related PitNETs that are resistant to medical treatments. To date, no increased incidence of aggressive tumors, and especially aggressive corticotroph tumors, has been reported in patients harboring these germline mutations. However, other germline mutations could lead to more aggressive forms.

A recent study reported three pituitary tumors in 910 patients harboring microsatellite instability due to Lynch syndrome. One patient had a large invasive nonfunctioning macroadenoma (histopathological analysis not available) and one patient developed a corticotroph pituitary carcinoma. More data are required to reach a conclusion on the relationship between an impaired MMR system and aggressive pituitary tumors, but a pituitary tumor which occurs in a patient with Lynch syndrome should be closely monitored.

In a cohort of corticotroph APTs and carcinomas, a loss of nuclear ATRX (alpha thalassemia/mental retardation syndrome X-linked) immunoreactivity was found in 32% of cases. This lack of ATRX protein expression resulted from loss-of-function mutations in the ATRX gene including nonsense mutations, frameshift indels, and large intragenic deletions. In this study, TP53 mutations were frequently associated with ATRX mutations. Mutations in TP53, a tumor suppressor gene with multiple functions, have been described in corticotroph APTs and carcinomas, including in Nelson’s syndrome. Additionally, TP53 mutations may constitute driver events in USP8-wild-type corticotroph tumors. In one study, tumors carrying TP53 mutations showed widespread copy number variants compared with tumors carrying USP8 mutations, suggesting higher genomic instability in the former.

5 | TREATMENT

5.1 | Temozolomide

Temozolomide is currently recommended by the European Society of Endocrinology (ESE) guidelines as the first-line chemotherapy, after the failure of standard treatment options (i.e., surgery, medical treatments, and radiotherapy), for pituitary carcinomas and aggressive pituitary tumors, irrespective of their histological subtype.

In the ESE survey, the response to first-line temozolomide of 73 corticotroph tumors, of which 19 were corticotroph carcinomas, was reported. Of these, 6 (8%) showed radiological complete response, 22 (30%) partial response, and 20 (27%) stable disease, while 25 (34%) progressed under first-line temozolomide (Figure 4). A clinically functioning status, along with concomitant radiotherapy administration and low (<10%) or intermediate (10%–50%) O6-methylguanine-DNA methyltransferase (MGMT) immunopositivity, were predictors of a better response to first-line temozolomide (Figure 2F). Low MGMT also predicted a better overall survival under first-line temozolomide, and possibly a better response to a second course of treatment. Indeed, it is noteworthy that relapse and/or progression were frequently encountered after an initial response, and...
that the response to a second course of treatment was less frequently favorable.5,54

Currently, the ESE guidelines recommend a treatment duration of first-line temozolomide of at least 6 months for responders. Evidence on the use of long-term temozolomide is still too scarce to enable formal recommendations, but clinical experience points towards the prolonged administration of the drug for as long as it remains effective and well-tolerated.55,56 In our clinical practice, we administer temozolomide at a standard dosage, as long as it is effective and, if complete response is seen, we then usually reduce dosage to a half-dose before stopping the drug.6

The most common adverse events (AEs) reported were fatigue, cytopenia, nausea, and vomiting. Headache, hypotension, edema, abnormal liver function tests, adrenal crisis, and hearing loss, have also been reported.3,5

5.2 | Immune checkpoint inhibitors (ICIs)

Seven corticotroph tumors, six of which were corticotroph carcinomas, have so far been treated using ICIs.57-61 The radiological response is summarized in Figure 4. Four functioning corticotroph carcinomas, two that received ipilimumab and nivolumab (followed by nivolumab alone), and two that received pembrolizumab, showed radiological partial response.57-61 This radiological partial response was accompanied by biochemical partial response in three of the cases, and by biochemical complete response in one case.57-59,61

One functioning corticotroph carcinoma that was treated with ipilimumab and nivolumab (followed by nivolumab alone) showed radiological stable disease, accompanied by biochemical partial response,60 while a silent corticotroph carcinoma that received pembrolizumab, showed radiological stable disease, but with clinically relevant tumor growth.61 Of note, the notion of “clinically relevant tumor growth” defines a tumor growth responsible for new/worsening/imminent neuro-ophthalmologic signs and symptoms; this notion is independent of the radiological assessment, that is, a “clinically relevant tumor growth” may be seen even in cases with radiological stable disease.6

The aggressive corticotroph tumor, which was functioning by the time pembrolizumab was administered, showed radiological and biochemical progressive disease.52

Of note, hypercortisolism was present in two cases, the tumor showing progressive disease and in one tumor showing stable disease,60,62 suggesting endogenous hypercortisolism might indeed lessen the efficacy of ICIs, since hypercortisolism was not noted in any of the responders. This is in line with the known immunosuppressive effect of glucocorticoids. It appears therefore important to try to achieve normal cortisol levels by using, for example, adrenal-targeted drugs.

AEs included fever, fatigue, rash, myalgia, anorexia, nausea, elevation of liver enzymes, and possibly progressive weight loss and hypophysitis.57-61

In most cancers, PDL1 immunohistochemistry and assessment of the tumor mutational burden (TMB) may be used to predict the response to immunotherapy. Tumors with high PDL1 immunexpression and TMB would be expected to be the most sensitive to immunotherapy. In the few available cases of corticotroph carcinomas treated by immunotherapy, PDL1 immunexpression was negative despite partial response or stable disease.50,61 In one case of stable disease, TMB was low. Analysis in larger cohorts is currently lacking to form a conclusion on the relevance of these theranostic markers.

5.3 | Bevacizumab

Eight corticotroph tumors, of which five were corticotroph carcinomas, have been treated to date with bevacizumab, an anti-VEGF monoclonal antibody, alone or in combination with temozolomide (two cases) with the radiological response being available for six cases.63-65

One functioning corticotroph carcinoma treated concomitantly with bevacizumab, temozolomide, and radiotherapy, showed radiological complete response. The associated biochemical response was not reported. The other corticotroph carcinoma, which was treated concomitantly with bevacizumab and temozolomide, was silent and showed radiological stable disease.63,65

Three corticotroph tumors that were treated with bevacizumab alone showed radiological stable disease,63 while one progressed.64 Their responses are shown in Figure 4. Two patients did not present any AEs65 while for the other cases this information was not available.63,64
5.4 | Other treatments

Three corticotroph tumors were treated using everolimus (an mTOR inhibitor), and showed approximately 5 months transient stability in one case, followed by progressive disease, and progressive disease was reported the other two cases.\textsuperscript{63,64}

Two corticotroph tumors were treated with peptide receptor radionuclide therapy, one of which showed radiological progressive disease, while in the second, the radiological response was not evaluated because the patient died due to elevated intracranial pressure shortly after the administration of peptide receptor radionuclide therapy.\textsuperscript{63}

One corticotroph carcinoma was treated with sunitinib (a multityrosine kinase inhibitor) and showed disease progression.\textsuperscript{64}

6 | Conclusion

To conclude, aggressive corticotroph tumors and carcinomas are challenging from their diagnosis to their therapeutic management. Despite limitations, initial pathology can help to identify pituitary tumors with malignant potential; however, clinical follow-up is still mandatory before initiating chemotherapy. Temozolomide is efficient as first-line treatment and ICIs may represent a good alternative for resistant corticotroph carcinomas. Despite the recent improvements in our knowledge, identification of early prognostic markers of tumor behavior, tumor response to treatment, and the optimal duration and sequence of treatments are still needed.

This article is part of an update series on the diagnosis and treatment of Cushings syndrome.\textsuperscript{66–82}

Author Contributions

Helene Lasolle: Data curation; writing - original draft; writing - review and editing. Alexandre Vasiljevic: Formal analysis; writing - original draft; writing - review and editing. Emmanuel Jouanneau: Validation; writing - review and editing. Mirela Ilie: Conceptualization; data curation; writing - original draft; writing - review and editing. Gerald Raverot: Conceptualization; data curation; writing - original draft; writing - review and editing.

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