Corticotroph pituitary carcinoma with skeletal metastases masquerading as ectopic ACTH syndrome: a long and winding road to diagnosis

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Summary

Pituitary carcinoma is a rare type of malignancy and only accounts for 0.1–0.2% of all pituitary tumours. Most pituitary carcinomas are hormonally active and they are mostly represented by corticotroph and lactotroph carcinomas. Corticotroph carcinoma can present as symptomatic Cushing's disease or can evolve from silent corticotroph adenoma which is not associated with clinical or biochemical evidence of hypercortisolism. We hereby present a case of a bone-metastasized corticotroph pituitary carcinoma masquerading as an ectopic adrenocorticotropic hormone (ACTH) syndrome in a patient with a history of a non-functioning pituitary macro-adenoma. Our patient underwent two transsphenoidal resections of the primary pituitary tumour followed by external beam radiation therapy. Under hydrocortisone substitution therapy she developed ACTH-dependent hypercortisolism without arguments for recurrence on pituitary MRI and without central-to-peripheral ACTH-gradient on inferior petrosal sinus sampling, both suggesting ectopic production. Ultimately, she was diagnosed with an ACTH-secreting vertebral metastasis originating from the primary pituitary tumour. This case report demonstrates the complex pathophysiology of pituitary carcinoma and the long diagnostic work-up. Certain features in pituitary adenoma should raise the suspicion of malignancy.

Learning points:

- The diagnosis of pituitary carcinoma can only be made based on documented metastasis, therefore, due to the often long latency period between the detection of the primary tumour and the occurrence of metastasis, the diagnostic work-up most often spans over multiple years.
- Pituitary carcinoma including corticotroph carcinoma is very rare in contrast to pituitary adenoma and only accounts for 0.1–0.2% of all pituitary tumours.
- Histopathology in pituitary adenoma should certainly accomplish the following goals: accurate tumour subtyping and assessment of tumoural proliferative potential.
- Repeated recurrence of pituitary adenoma after surgical resection, a discrepancy between biochemical and radiological findings, resistance to medical and radiation therapy, and silent tumours becoming functional are all hallmarks of pituitary carcinoma.
- Silent corticotroph adenomas are non-functioning pituitary adenomas that arise from T-PIT lineage adenohypophyseal cells and that can express adrenocorticotropic hormone on immunohistochemistry, but are

not associated with biochemical or clinical evidence of hypercortisolism. Silent corticotroph adenomas exhibit a more aggressive clinical behaviour than other non-functioning adenomas.

- Treatment options for corticotroph carcinoma include primary tumour resection, radiation therapy, medical therapy, and chemotherapy. Sometimes bilateral adrenalectomy is necessary to achieve sufficient control of the cortisol excess.

Background

Pituitary carcinoma is an uncommon type of malignancy and is defined as a tumour of adenohypophyseal origin with either non-contiguous spread and/or metastasis to sites distant from the sellar region (1, 2, 3). In contrast to pituitary adenoma, which is a common intracranial tumour, pituitary carcinoma is a very rare entity and only accounts for 0.1–0.2% of all pituitary tumours (1, 4, 5). The diagnosis of pituitary carcinoma can only be established if cerebrospinal or systemic metastasis of a pituitary tumour has occurred and cannot be made based on pituitary imaging or biopsy alone (3, 4). In a considerable number of cases, distant metastasis of a pituitary tumour is only detected on autopsy, therefore the reported prevalence could be an underestimation (4).

Similar to pituitary adenoma, the clinical features of pituitary carcinomas are caused by excess hormonal production and/or mass effect on adjacent structures. Most pituitary carcinomas are hormonally active: the most common are prolactin (PRL)-secreting tumours and adrenocorticotropic hormone (ACTH)-secreting tumours(2). ACTH-secreting carcinoma can present as Cushing's disease or can evolve from silent corticotroph adenoma, which initially does not present with symptomatology related to cortisol excess. There are only a limited number of cases in the medical literature describing corticotroph carcinoma (6). We hereby present the case of a corticotroph carcinoma masquerading as an ectopic ACTH syndrome due to ACTH-producing skeletal metastases in a patient with a history of a non-functioning pituitary adenoma.

Case presentation

A 44-year-old woman consulted our endocrinology outpatient clinic for a second opinion in October 2017. Eight years earlier, in December 2009, she had been diagnosed with a non-functioning pituitary macro-adenoma resulting in central hypothyroidism and hypogonadotropic hypogonadism. In January 2010, she underwent transsphenoidal resection of the pituitary tumour with histopathology examination compatible with pituitary adenoma (Fig. 1). Postoperative MRI 3 months later showed a complete resection. After the operation, she developed central adrenal insufficiency, central diabetes insipidus, and growth hormone deficiency. Therefore, therapy with oral hydrocortisone (10 mg – 5 mg – 10 mg daily), intranasal desmopressin (10 µg daily), an oral combined contraceptive pill (ethinylestradiol 0.015 mg – gestodene 0.06 mg), and subcutaneous growth hormone substitution therapy (somatropin 0.3 mg daily) was initiated in addition to oral thyroid replacement therapy (levothyroxine 150 µg daily). In March 2012, on yearly pituitary follow-up MRI, tumoural recurrence was detected (Fig. 2A and B). Consequently, a new transsphenoidal resection was performed followed by adjuvant radiotherapy. Afterwards, no signs of recurrence were detected on yearly follow-up. In October 2017, she started complaining of progressive weight gain and decided to come to our endocrinology outpatient clinic for a second opinion. She presented with morbid obesity (BMI 41.8 kg/m²), a rounded facies, and arterial hypertension (152/93 mmHg) on physical examination.
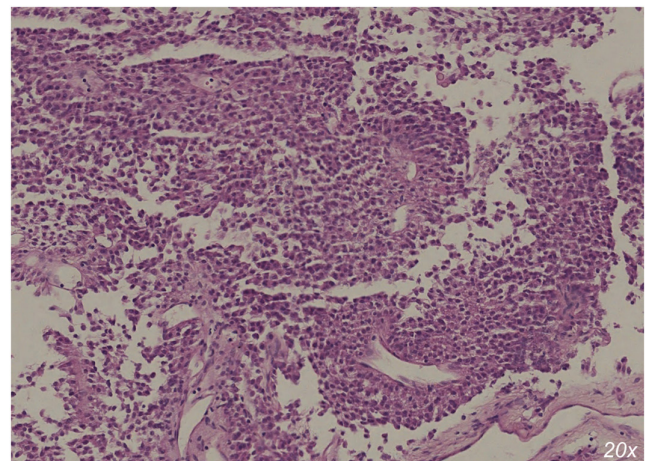

Figure 1
Pituitary tumor resected in 2010. Histopathology examination was compatible with pituitary adenoma. Hematoxylin and eosin stain (20×).
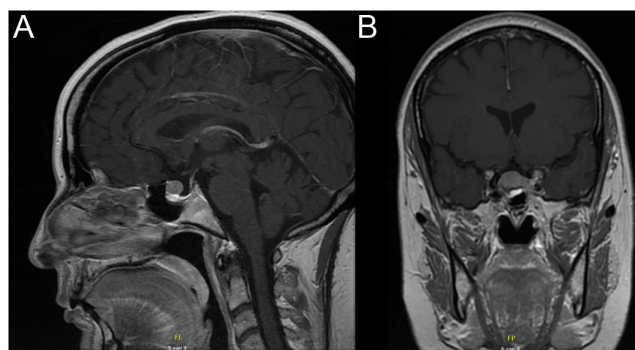
Figure 2
Gadolinium (Gd)-enhanced T1 weighted sagittal MRI image (A) and coronal MRI image (B) showing recurrence of pituitary macro-adenoma.

Investigation

Laboratory test results under hydrocortisone substitution therapy showed elevated morning cortisol levels (993.17 nmol/L; 138–635 nmol/L) as expected, but also a high level of ACTH (25.30 pmol/L; 2.2–13.3 pmol/L) despite exogenous cortisol substitution. After discontinuation of hydrocortisone, laboratory testing to evaluate hypercortisolemia was repeated; 24-h urinary-free cortisol (1453.4 µg/24 h; 36.0–137.0 µg/24 h) and late-night salivary cortisol (475.9 nmol/L; <50 nmol/L) were elevated. A high-dose dexamethasone suppression test suggested ectopic ACTH secretion (Table 1). Additional testing also revealed new onset secondary diabetes mellitus (HbA1c 53 mmol/mol; <42 mmol/mol). High-resolution gadolinium-enhanced pituitary MRI showed no recurrence of the pituitary tumour. Inferior petrosal sinus sampling again suggested ectopic ACTH syndrome, due to the absence of central-to-peripheral ACTH gradient (Table 2). CT imaging of the thorax and abdomen showed no presence of tumoural processes. The tissue specimens of the two transsphenoidal resections of the previously assumed non-functioning pituitary macro-adenoma were re-evaluated. Immunohistochemistry stains on the preserved specimens were positive for chromogranin A and ACTH. The non-functioning pituitary adenoma diagnosed in 2009 was now considered to be a silent corticotroph adenoma. However, the origin of the current ectopic ACTH-production could still not be found. A few months later an asymptomatic compression fracture of the ninth thoracic vertebra was incidentally detected on a lumbar CT scan performed to evaluate consolidation of a previously diagnosed osteoporotic compression fracture of the L1 vertebra. On these CT scan images, the radiological features of the T9 compression fracture were suggestive for a pathological fracture due to a lytic bone lesion (Fig. 3A and B). Nevertheless, an oncological PET scan could not identify a primary tumour. At this point, the differential diagnosis consisted of a primary bone tumour or a skeletal metastasis of a not yet identified malignant tumour. Considering the source of the ectopic ACTH secretion still had not been discovered, a biopsy of the T9 vertebra was performed. Histopathological examination of the obtained tissue suggested a neuroendocrine proliferation with a diffuse expression of synaptophysin and an elevated Ki-67 index (±10%). Additional immunohistochemical examination showed 10% positivity for ACTH with the expression of somatostatin receptor subtype 2A in the ACTH-positive cells. (Fig. 4A, B, and C). O-6-methylguanine-DNA methyltransferase (MGMT) promoter hypermethylation analysis revealed no hypermethylation of the promotor region of the *MGMT*-gene. The obtained tissue of the T9 vertebra was compared to the resection pieces from 2010 and 2012. Morphologically, the tumoural cells appeared identical. This suggested that our patient's initially silent corticotroph pituitary adenoma had metastasized to bone, which implicated the diagnosis of a corticotroph pituitary carcinoma. After this finding, a 68Gallium-DOTANOC scan was performed during disease staging and showed a hotspot in the T9 vertebra. It also revealed a second skeletal hotspot in the sacrum (Fig. 5).

Treatment

Due to the rapidly progressive clinical course and the still unknown origin of the ectopic ACTH-production, we started oral ketoconazole therapy and performed

Table 1 Initial laboratory findings.

Parameters	Results	Reference range
Serum cortisol 08:00 h (nmol/L)	993.17	138.0–635.0
Plasma ACTH 8:00 h (pmol/L)	25.30	2.2–13.3
24-h urinary-free cortisol (µg/day)	1453.4	36.0–137.0
Cortisol 8:00 h after 8 mg DST (nmol/L)	893.85	<50
Percentage of cortisol suppression after 8 mg DST (%)	10	
Late night salivary cortisol (nmol/L)	475.9	<50

ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression test.

Table 2 Inferior sinus petrosus sampling.

Time	ACTH				
	Left petrosal	L/P	Right petrosal	R/P	Peripheral
0	31.46	1.075	29.26	0.978	29.92
3	32.78	1.137	32.12	1.115	28.82
6	31.46	1.092	32.56	1.130	28.82
9	34.76	1.317	31.90	1.208	26.40

ACTH, adrenocorticotropic hormone (in pmol/L); Time 0 min: i.v. injection of 100 μg corticotrophin-releasing hormone (CRH).

semi-urgent bilateral adrenalectomy in the period before the T9 vertebral biopsy. After laparoscopic bilateral adrenalectomy, oral hydrocortisone therapy was resumed. Post-operatively 24-h urinary-free cortisol level decreased to 185.7 μg/24 h.

Finally, after that the diagnosis of the ACTH-producing skeletal metastasis had been confirmed, external beam radiation therapy consisting of 30 sessions of 1.8 Gy and subcutaneous somatostatin analogue therapy (lanreotide 120 mg monthly) were initiated following neuroendocrine oncology multidisciplinary team meeting. Chemotherapy with capecitabine and temozolomide was considered, but due to the low burden of the disease, the decision was made to treat the two isolated metastases locoregionally by external beam radiotherapy and to reserve temozolomide for if the carcinoma would become more clinically aggressive.

Outcome and follow-up

Three years later in 2020, after initial normalization of ACTH, our patient's laboratory results once again showed

Figure 3
CT sagittal image (A) and coronal image (B) of the thoracolumbar spine. A compression fracture of the ninth thoracal vertebra can be seen with extensive bony destruction, besides an older compression fracture of the first lumbar vertebra.

increasing ACTH levels justifying the performance of a new full-body MRI. On this MRI a third skeletal metastasis in the sternum was detected and local stereotactic radiotherapy was initiated. Unfortunately, during radiotherapy treatment, our patient stopped coming to follow-up visits and therefore no additional therapy could be initiated. She passed away in the summer of 2021.

Discussion

Our case report describes a silent corticotroph adenoma transforming into a corticotroph carcinoma masquerading as an ectopic ACTH syndrome due to ACTH-secreting skeletal metastases. Our case parallels other corticotroph carcinoma cases which have been reported in the medical literature with similar clinical features and a comparable disease course (6). Repeated recurrence of pituitary adenoma after surgical resection, a discrepancy between biochemical and radiological findings, resistance to conventional medical and radiation therapy, and silent tumours becoming functional are hallmarks of corticotroph carcinoma (2).

The diagnosis of pituitary carcinoma can only be made once metastasis has occurred. On histopathological examination, conventional signs of malignancy like cellular and nuclear pleomorphism, hypercellularity, foci of necrosis, invasive spread in surrounding tissues, increased mitotic activity, nuclear hyperchromatism, and increased nuclear/cytoplasmic ratio, are not necessarily present and cannot differentiate between locally aggressive pituitary adenoma or pituitary carcinoma (3, 4, 6). The latency period between detection of the primary tumour in pituitary carcinoma and occurrence of metastasis is variable, with latencies of four months to thirty years being reported (1, 5). But as previously mentioned, sometimes the diagnosis of metastasis is only made post-mortem (4). The mean latency period of metastatic dissemination in corticotroph carcinoma is longer in comparison to PRL-secreting carcinoma, respectively, 9.5 years in corticotroph carcinoma vs 4.7 years in lactotroph (5). Metastasis can be limited to the craniospinal axis but can also spread to distant organ systems. Metastasis outside of the craniospinal axis mostly occurs by hematogenous pathway to the liver or bone, but metastasis to the ovaries and lungs has also been described (5). Although most operated pituitary adenoma never metastasize, it is noteworthy that in pituitary carcinoma metastasis occurring without prior surgical intervention is rare (5). It is still uncertain whether surgery of the primary sellar tumour facilitates metastasis if the primary tumour already has a predisposition to exhibit
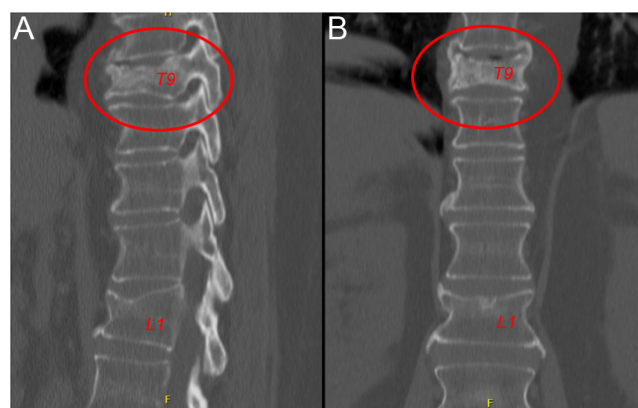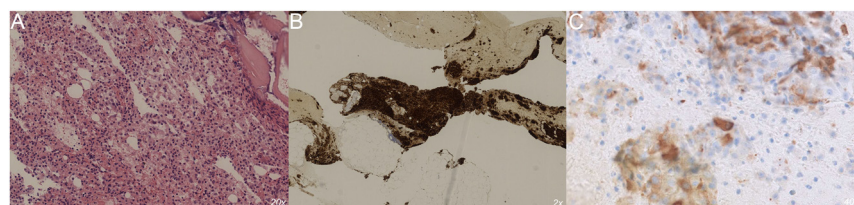
Figure 4
Biopsy of the vertebral lesion. (A) Presence of bone marrow foreign cells on haematoxylin and eosin stain (20×). (B) Synaptophysin immunohistochemical staining was diffusely and strongly positive in all tumoral cells of the vertebral lesion. Immunohistochemical staining for chromogranin showed similar results (2×). (C) Positive immunohistochemical staining for ACTH of the tumoral cells (40×).

a more aggressive character. Our patient suffered from skeletal metastases to the vertebra, sacrum, and sternum, which occurred after repeat transsphenoidal resection of the primary pituitary tumour.

Some subtypes of pituitary adenoma are classified as high-risk by the WHO classification due to their clinical aggressive behaviour, such as silent corticotroph adenoma (3, 7). Silent corticotroph adenoma is a type of non-functioning adenoma arising from adenohypophyseal cells of the T-PIT lineage that can demonstrate positive immunohistochemistry for ACTH but does not present with biochemical or clinical evidence of hypercortisolism (3, 7). A silent corticotroph adenoma most often presents as a non-functioning macro-adenoma with pituitary hormone deficiencies and local mass effect. Diagnosis can only be made after histopathological examination of the resected tumour tissue. In rare cases, and suggestive for pituitary carcinoma, silent corticotroph adenomas can become functional, which was the case in our patient (2).

Corticotroph carcinoma is a rare entity and therefore optimal therapeutic management is still a point of discussion. In 2018, the European Society of Endocrinology (ESE) published clinical practice guidelines for the management of aggressive pituitary tumours and carcinomas (8). As already stated by Kaltsas et al in their review about the management of pituitary carcinomas, a multidisciplinary approach is warranted with a combination of surgical resection, radiation therapy, medical therapy, and chemotherapy (4). The mainstay of treatment of pituitary carcinoma is tumoural resection

Figure 5
68Gallium-DOTANOC scan coronal image. A skeletal hotspot can be seen in the ninth thoracal vertebra (A) and the left sacrum (B).

with a transsphenoidal approach to reduce the local mass effect and to obtain a histopathological characterization of the tumour. Histopathology examination in pituitary adenoma should accomplish an accurate tumour subtyping, a correct assessment of tumoural proliferative potential using mitotic count and Ki-67 index, and an evaluation of clinical parameters such as tumour invasion (3, 8). In our case, in 2010, when the first histopathological examination of the resected pituitary adenoma was performed, the proliferative markers were not evaluated and hormone positivity was only evaluated at a later stage. In retrospect, it is possible that if a correct characterization of the first specimen of the pituitary adenoma had been performed, this tumour's potential for aggressive behaviour would have been detected earlier with a possible impact on therapeutic management.

In pituitary carcinoma, primary surgery is often not curative with a high rate of tumoural recurrence which often leads to repeat surgery, as was the case in our patient. Other treatment options for persistent or recurrent hypercortisolism after surgical resection are radiation therapy, medical therapy, and bilateral adrenalectomy (9). These treatment modalities can also be applied in the first place when surgery is not feasible and/or contraindicated. Radiation therapy can be administered conventionally with fractionated doses or by using stereotactic radiotherapy. Medical therapies that can help manage Cushing's disease are steroidogenesis inhibitors, dopamine D2 receptor agonists, or somatostatin analogue therapy. Bilateral adrenalectomy is a treatment option reserved for patients who do not respond adequately to the therapies mentioned above (9). The advantage of adrenalectomy is that rapid control of hypercortisolism can be achieved, the pitfall is that it leads to a permanent primary adrenal insufficiency resulting in a lifelong need for adrenal replacement therapy.

Specifically for pituitary carcinoma, chemotherapeutic regimens consisting of temozolomide are given with satisfying results (1, 2, 8, 10). After the failure of standard treatment, the ESE guidelines recommend temozolomide as the recommended first-line chemotherapy drug (2, 8).
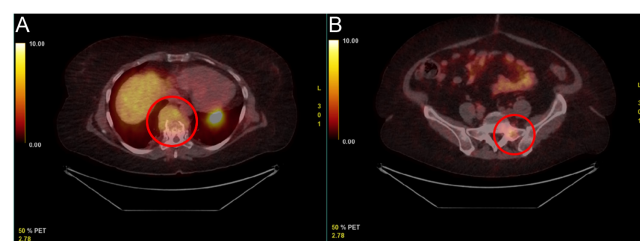
Temozolomide is a peroral alkylating chemotherapeutic drug that causes irreversible DNA damage and cell death due to the methylation of DNA. A DNA-repair enzyme, MGMT, can potentially counteract its effects, therefore tumours with a low MGMT expression on immunohistochemistry have a better response to treatment (2, 8, 10). Radiosensitizing effects of temozolomide have also been reported, resulting in a better response to radiotherapy after chemotherapy course, leading to the development of the Stupp protocol with concomitant use of temozolomide and radiotherapy (2, 8, 10). However, the optimal duration of therapy with temozolomide is not well studied yet. Noteworthy, too early discontinuation of temozolomide therapy is associated with a higher risk of tumoural progression and a diminished response to a repeat course of temozolomide (10). In our patient, the decision was made to treat the two isolated metastases with a locoregional approach consisting of external beam radiotherapy. Chemotherapy with temozolomide was not initiated at this point. This decision was made on a multidisciplinary team meeting with the argument that since there are no evidence-based treatments available for patients progressing or recurring after therapy with temozolomide, starting chemotherapy would better be reserved for if the tumour would become more aggressive. The ESE guidelines also recommend locoregional therapeutic approaches in case of localized low-burden disease (8).

The use of peptide receptor radionuclide therapy (PRRT) has been reported in a few cases of pituitary carcinoma with varying results if treatment with temozolomide fails. Further research to determine the clinical utility of molecular-based therapies and immunotherapy in pituitary carcinoma is still ongoing (2).

Our case illustrates well the convoluted diagnostic work-up of pituitary carcinoma, which can only be diagnosed once the presence of metastasis of the primary pituitary tumour has been confirmed. The diagnostic process is further impeded due to the rarity of this type of malignancy and the often long latency period between the detection of the primary tumour and the occurrence of metastasis. Our patient with a medical history of non-functioning macro-adenoma, who initially presented with central adrenal insufficiency after resection of her pituitary adenoma, developed ACTH-dependent hypercortisolism while being treated with exogenous cortisol substitution therapy. This patient's apparent ectopic ACTH syndrome eventually turned out to be caused by multiple ACTH-secreting skeletal metastases of an initially silent corticotroph adenoma progressing to a corticotroph pituitary carcinoma. This case also certainly highlights the importance of a complete histopathology examination of pituitary adenoma consisting of correct tumour subtyping and assessment of proliferative potential.

Author contribution statement

Dr E Van Mieghem drafted the manuscript and did part of the literature search. Dr V Intan-Goey helped writing the first draft of the article. Dr W Buffet is a pathologist and performed immunohistochemical staining of the resection pieces. Prof Dr M Lammens is head of Pathological anatomy of the University Hospital of Antwerp where ACTH-staining of the resection pieces was performed. Dr P Van Loo is the neurosurgeon who performed the biopsy of the T9 vertebra. Dr P Abrams is head of endocrinology of the GZA Hospitals, the primary attending physician of this patient, and did part of the literature search. All authors reviewed the manuscript and approved this version to be published.

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