





Medullary thyroid cancer with ectopic Cushing's syndrome: A multicentre case series

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Abstract

Objective: Ectopic Cushing's syndrome (ECS) induced by medullary thyroid cancer (MTC) is rare, and data on clinical characteristics, treatment and outcome are limited.

Design: Retrospective cohort study in three German and one Swiss referral centres.

Patients: Eleven patients with MTC and occurrence of ECS and 22 matched MTC patients without ECS were included.

Measurements: The primary endpoint of this study was the overall survival (OS) in MTC patients with ECS versus 1:2 matched MTC patients without ECS.

Results: The median age at diagnosis of ECS was 59 years (range: 35–81) and the median time between initial diagnosis of MTC and diagnosis of ECS was 29 months (range: 0–193). Median serum morning cortisol was 49 µg/dl (range: 17–141, normal range: 6.2–18). Eight (73%) patients received treatment for ECS. Treatment of ECS consisted of bilateral adrenalectomy (BADX) in four (36%) patients and adrenostatic treatment in eight (73%) patients. One patient received treatment with multityrosine kinase inhibitor (MKI) to control hypercortisolism. All patients experienced complete resolution of symptoms of Cushing's syndrome and biochemical control of hypercortisolism. Patients with ECS showed a shorter median OS of 87 months (95% confidence interval [95% CI]: 64–111) than matched controls (190 months, 95% CI: 95–285). Of the nine deaths, four were related to progressive disease (PD). Four patients showed PD as well as complications and comorbidities of hypercortisolism before death.

Conclusion: This study shows that ECS occurs in advanced stage MTC and is associated with a poor prognosis. Adrenostatic treatment and BADX were effective systemic treatment options in patients with MTC and ECS to control their hypercortisolism. MKI treatment achieved complete remission of hypercortisolism and sustained tumour control in one treated case.

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KEYWORDS

ectopic Cushing's syndrome, hypercortisolism, medullary thyroid cancer, multityrosine kinase inhibitors, outcome, RET inhibitors, treatment

1 | INTRODUCTION

Medullary thyroid cancer (MTC) arises from calcitonin-producing parafollicular C-cells of the thyroid gland and accounts for 2%–5% of all thyroid malignancies.¹ In about 25% of cases, MTC occurs in a hereditary manner as a part of multiple endocrine neoplasia type 2 (MEN2) caused by oncogenic germline *RE*arranged during *Transfection* (RET)-mutations. Up to 65% of patients with the sporadic disease have somatic RET-mutations, among which *RET*M918T is the most common and associated with adverse outcome.^{2–5} At diagnosis, cervical lymph node metastases are present in about half of patients and distant metastases in around 10% of MTC patients.⁶ While the localized disease has a 10-year disease-specific survival (DSS) of 96%, 10-year DSS is only 44% in cases with distant metastases.^{7–9}

Besides calcitonin and carcinoembryonic antigen (CEA), C-cells may also ectopically secrete corticotropin-releasing hormone (CRH) or adrenocorticotrophic hormone (ACTH). Cushing's syndrome (CS) due to ectopic CRH or ACTH secretion induced by MTC is rare and data on clinical characteristics, treatment and outcome are limited and mostly from case studies. In a retrospective study of 1640 adult patients with MTC, ectopic Cushing's syndrome (ECS) due to ACTH secretion was reported in only 0.6% of patients, whereas previous studies reported a higher prevalence, possibly due to selection bias.^{10–12} ECS mostly occurs in metastatic cases and significantly impairs prognosis: around 50% of the mortality in patients with ECS has been attributed to complications of hypercortisolism.¹² Diagnosis of ECS is difficult and includes a combination of clinical assessment, dynamic biochemical tests (e.g., 24 h urinary-free cortisol, midnight salivary cortisol, 1 and 8 mg dexamethasone suppression test), inferior petrosal sinus sampling (IPSS) and multimodal imaging.¹³

This retrospective study aims at describing clinical characteristics, treatment and prognosis of 11 patients with MTC and ECS at 3 German and 1 Swiss tertiary care centres and to illustrate effective treatment in this ultrarare condition.

2 | PATIENTS AND METHODS

2.1 | Setting

This registry study was conducted as part of the German Study Group for Rare Malignant Tumours of the Thyroid and Parathyroid Glands. Data were obtained from records of patients diagnosed with MTC between 1990 and 2020 and concomitant ECS diagnosed between 1995 and 2020 in three German and one Swiss tertiary care centres. All patients provided written informed consent and the study was approved by the ethics committee of the University of Würzburg (96/13) and subsequently by the ethics committees of all participating centres.

2.2 | Data acquisition

Eligible patients were 11 adults with histopathological evidence of MTC and the diagnosis of ECS at initial diagnosis (synchronous CS) or during the course of disease (metachronous CS). This group was matched with 22 patients with histologically confirmed MTC without evidence of ECS by sex, age at MTC diagnosis (± 5 years), tumour stage and calcitonin doubling time (CDT).

The diagnosis of ECS was established by standard endocrine testing according to international guideline recommendations,¹⁴ local good clinical practice procedures and laboratory assays in participating centres. The primary endpoint of this study was the assessment of overall survival (OS) in MTC patients with ECS from the date of MTC-diagnosis and the date of ECS-diagnosis versus matched MTC patients without ECS (1:2 ratio). The secondary endpoints were assessment of progression-free survival (PFS) and efficacy of multityrosine kinase inhibitors (MKIs) treatment (based on routine clinical imaging in analogy to RECIST 1.0 and 1.1). Treatment and follow-up of patients were performed according to the local practice of participating centres. Efficacy was assessed locally by imaging (positron emission tomography/computed tomography [PET/CT], CT, magnetic resonance imaging [MRI] of the liver and bone scintigraphy) and measurement of serum calcitonin and CEA levels every 3–6 months. Clinical data were recorded by trained personnel at all sites. Tumour stage was defined according to the American Joint Committee on Cancer TNM classification, seventh edition,¹⁵ based on clinical and histopathological assessments.

2.3 | Statistical analysis

PFS and OS probabilities were estimated using the Kaplan–Meier method. The log-rank test was not used to test the difference between the study group and the control group due to the paired sample design. For the comparison of nonnormally distributed data, we used the Mann–Whitney *U* test. *p* Values less than .05 were considered statistically significant. Statistical analyses were performed with SPSS Version 26 (IBM).

3 | RESULTS

3.1 | Clinical characteristics of patients with ECS

Eleven patients (five male and six female) with histopathological evidence of MTC with ECS in three German and one Swiss tertiary care centres were included. Twenty-two controls with histologically confirmed MTC without the diagnosis of ECS matched by sex, age at MTC

TABLE 1 Patient characteristics of the study cohort

Patient characteristics	Number of ECS patients (total number)	Number of control groups (total number) ^a	p-Value
Number of patients	11	22	
Matched factors			
Male sex	5	10	1.00
Median age at first diagnosis (years) (range)	49 (31–81)	46 (30–80)	1.00
UICC stage at first diagnosis			.9
II	0	1 (n = 20)	
III	3 (n = 10)	3 (n = 20)	
IV	7 (n = 10)	17 (n = 20)	
Median calcitonin doubling time before ECS (months) (range)	8 (1–30, n = 9)	7 (2–31, n = 11)	1.00
Other factors			
Median age at diagnosis of ECS (years) (range)	59 (35–81)		
RET mutation status			
Germline RET mutation	3 (n = 10)	1 (n = 19)	
Somatic RET mutation (no germline mutation)	2 (n = 6)	12 (n = 16)	
Somatic RET mutation (unknown germline mutation)	1 (n = 6)	2 (n = 16)	
Lymphatic metastasis at first diagnosis	10 (n = 10)	18 (n = 20)	
Distant metastasis at first diagnosis	6 (n = 8)	9 (n = 16)	
Lung	4	4	
Liver	5	4	
Mediastinum	3	3	
Bone	1	3	
Treatment before the diagnosis of ECS			
Initial thyroidectomy	9		
Surgery for metastases	5 (n = 10)		
Peptide receptor radionuclide therapy before ECS	1 (n = 10)		
Chemotherapy before ECS	2 (n = 10)		
Local radiation therapy before ECS	1 (n = 10)		
Radiation therapy of metastatic sites before ECS	2 (n = 10)		
MKI treatment before ECS			
Vandetanib	1		
Cabozantinib	1		

Abbreviations: ECS, ectopic Cushing's syndrome; MKI, multitargeted tyrosine kinase inhibitors; MTC, medullary thyroid cancer; RET, rearranged during transfection; UICC, Union for International Cancer Control.

^aMatched by sex, age at MTC diagnosis (± 5 years), tumour stage and median calcitonin doubling time.

diagnosis (± 5 years), tumour stage and CDT were enrolled. Baseline clinical characteristics of the study population and the control group are shown in Table 1. In patients with ECS, median follow-up from initial MTC diagnosis was 6.3 years (range: 0–17) and median follow-up from diagnosis of ECS 7 months (range: 0–110). Median age at initial diagnosis of sporadic MTC was 45 (range: 31–67, $n = 7$) and 52 years (range: 35–55, $n = 3$) for patients with germline *RET* mutant MTC.

At the time of initial diagnosis of MTC, three patients had tumour-stage III disease and seven patients had tumour-stage IV disease (mediastinal lymph nodes $n = 3$, lung $n = 4$, liver $n = 5$ and bone $n = 1$). In one case tumour stage was not obtainable.

By the time of ECS diagnosis, eight (73%) patients had local regional lymph node metastases, eleven (100%) patients had distant metastases (mediastinal lymph nodes 4 [36%], lung 7 [64%], liver 10

[91%], bone 5 [45%]). ACTH staining was performed in one thyroid (1/9) and one hepatic (1/5) tissue sample. Immunohistochemistry for ACTH revealed ACTH-positive cells in one tumour sample. CRH staining was not performed.

The median age at diagnosis of metastatic disease was 55 years (range: 33–81) and five (45%) patients had distant metastases at diagnosis of MTC. In patients with metastatic disease, the median time between initial diagnosis and evidence of metastatic disease was 10 months (range: 0–183).

At the end of data collection, nine (82%) patients had died, none of the patients was lost to follow-up. Of the nine deaths, four were related to progressive disease (PD). Four patients showed PD as well as complications of hypercortisolism before death. Complications of CS were psychosis with suicidal thoughts, abdominal wall abscess, severe hypokalemia <3.0 mmol/L and hemodynamically relevant bleeding after liver puncture, spontaneous bleeding in pneumothorax/peritoneum, thrombosis of superficial veins considered to be due to thrombocytopenia and activated coagulation despite prophylactic and later-on half-therapeutic heparinization. Data of one (11%) patient were not obtainable.

3.2 | Clinical symptoms and hormonal investigations of ECS

Clinical and laboratory characteristics are shown in Table 2. At the time of ECS diagnosis, the most frequent clinical signs of cortisol excess were proximal muscle weakness, diabetes mellitus and a cushingoid appearance.

CDT was 8 months (range: 1–30) before the diagnosis of ECS. The median age at diagnosis of ECS was 59 years (range: 35–81) and the median time between initial diagnosis and diagnosis of ECS was 29 months (range: 0–193). Most patients (10; 91%) presented with meta-chronous CS. Median urinary-free cortisol, serum cortisol and plasma ACTH were elevated, all patients receiving a low-dose and/or high-dose dexamethasone suppression test showed a lack of cortisol suppression. In all 11 patients, at least one test result was highly suggestive of CS with concomitant clinical features. Five patients received MRI scans to rule out pituitary adenoma. Two patients received somatostatin receptor imaging by PET before the diagnosis of ECS, none of the patients received somatostatin receptor scintigraphy/single-photon emission computed tomography or PET after the diagnosis of ECS.

One patient underwent CRH testing, which showed absent ACTH increase consistent with an ectopic source of ACTH. No patient received IPSS to diagnose the ectopic origin of CS.

As an exploratory analysis, ECS patients were divided into a group with a time between ECS diagnosis and death <12 months and a group with a time between ECS diagnosis and death ≥12 months. Patients who died during the first year after diagnosis of ECS lacked typical cushingoid appearance ($p = .021$), had lower median potassium values (2.7 vs. 3.6 mmol/L) and significantly higher serum morning cortisol ($p = .009$) compared to patients with a time between ECS diagnosis and death ≥12 months.

TABLE 2 Clinical and laboratory characteristics of ectopic Cushing's syndrome

	Number of patients (total number)
Clinical characteristics at ECS diagnosis	
Proximal muscle weakness	8 ($n = 9$)
Diabetes mellitus	6 ($n = 11$)
Cushingoid appearance	4 ($n = 9$)
Weight gain	3 ($n = 7$)
Hypertension	3 ($n = 9$)
Infection (pneumonia)	3 ($n = 11$)
Hyperlipidemia	1 ($n = 4$)
Osteoporosis	1 ($n = 4$)
Skin atrophy	2 ($n = 8$)
Psychiatric disorder	1 ($n = 10$)
Deep vein thrombosis and pulmonary embolism	0
Laboratory characteristics at ECS diagnosis	
Median plasma ACTH, pg/ml (normal range: 5–60) (range)	131 (8–201, $n = 11$) ^a
Median serum morning cortisol, µg/dl (normal range: 6.2–18) (range)	49 (17–141, $n = 11$) ^a
Median 24 h urinary-free cortisol, µg/dl (normal range ≤ 83 µg/24 h) (range)	139 (42–10,331, $n = 5$) ^a
Failure to suppress to 1 mg dexamethasone	5 ($n = 5$) ^a
Failure to suppress to 8 mg dexamethasone	2 ($n = 2$) ^{a,b}
Median potassium, mmol/L (normal range: 3.5–5.1) (range)	3.3 (2.1–4.4, $n = 10$) ^a
Median calcitonin level (pg/ml) at ECS diagnosis (normal range ≤ 10) (range)	14,855 (415–200,000)
Median CEA level (ng/ml) at ECS diagnosis (normal range depending on age and smoking status ^b) (range)	634 (34–2094)

Abbreviations: ACTH, adrenocorticotropic hormone; CEA, carcinoembryonic antigen; ECS, ectopic Cushing's syndrome.

^aTotal number of patients receiving this laboratory/dynamic biochemical test.

^bAll subjects 20–69 years 95th percentile 4.7, only ≥40 years 95th percentile 5.2; nonsmokers (past/never smokers) 20–69 years 95th percentile 3.8, only ≥40 years 95th percentile 5.0; smokers (current) 20–69 years 95th percentile 5.5, only ≥40 years 95th percentile 6.5.

3.3 | Therapy of ECS

Eight (73%) patients received specific treatment for hypercortisolism. Three patients did not receive any treatment for excessive cortisol and the best supportive care was the chosen management.

TABLE 3 Treatment characteristics of ectopic Cushing's syndrome

	Number of patients (total number of patients receiving specific treatment for hypercortisolism)
Treatment characteristics	
Adrenostatic treatment	8 (n = 8)
Before bilateral adrenalectomy	4
Without bilateral adrenalectomy	4
Bilateral adrenalectomy	4 (n = 8)
Characteristics of adrenostatic treatment	
Ketoconazole	2 (n = 8)
Duration in days	13 and 23
Starting dose in mg	400 and 1200
Discontinuation due to TEAE	0
Mitotane	1 (n = 8)
Median duration in days	30
Median starting dose in mg	3000
Discontinuation due to TEAE	1
Metyrapone	4 (n = 8)
Median duration in months (range)	4 (0–6)
Median starting dose in mg (range)	1550 (1500–4250)
Discontinuation due to TEAE	0
Ketoconazole (in combination with metyrapone)	1 (n = 8)
Median duration in months	4
Median starting dose in mg	400
Discontinuation due to TEAE	1
TEAE of adrenostatic treatment	
Elevated liver function tests	4 (n = 8)
Infections	2 (n = 8)
Changes in blood picture (anaemia, thrombocytopenia)	1 (n = 8)
Decreased appetite/weight loss	1 (n = 8)
Nausea	1 (n = 8)
Skin rash	1 (n = 8)
MKI treatment to control ECS	
Vandetanib	1 (n = 8)
MKI treatment after control of hypercortisolism	
Vandetanib	2 (n = 8) ^a
Cabozantinib	1 (n = 8) ^a

(Continues)

TABLE 3 (Continued)

	Number of patients (total number of patients receiving specific treatment for hypercortisolism)
RET-inhibitors (selpercatinib and pralsetinib)	1 (n = 8)
Median age at MKI initiation (range)	60 (36–66)
Median months between first diagnosis and MKI initiation (range)	61 (11–189)

Abbreviations: ECS, ectopic Cushing's syndrome; MKI, multitargeted tyrosine kinase inhibitors; TEAE, treatment-emergent adverse events.

^aOne patient received vandetanib and cabozantinib, subsequently.

Characteristics of ECS treatment are shown in Table 3. Treatment of ECS consisted of bilateral adrenalectomy (BADX) in four of eight patients previously treated with adrenostatic therapy. None of the patients was referred to BADX without prior medical treatment. With appropriate replacement treatment, no patient experienced an adrenal crisis after BADX. None of the patients received somatostatin analogues for the treatment of ECS. As adjunct treatment of CS, four (36%) patients were treated with a proton pump inhibitor, three (27%) patients received anticoagulant prophylaxis and two (18%) patients received a pneumocystis jirovecii pneumonia chemoprophylaxis.

All patients experienced complete resolution of symptoms of CS and biochemical control of hypercortisolism state.

3.4 | Survival

Median OS from diagnosis of ECS was 14 months (95% confidence interval [95% CI]: 0–44). Median OS from diagnosis of MTC was 87 months (95% CI: 64–111) in ECS patients and 190 months (95–285) in controls without ECS (Figure 1). As the mean observation time of control patients, with one exception, was longer than the time to ECS of the corresponding ECS patients, we can exclude a relevant immortal time bias in the survival comparison of ECS versus controls without ECS. Median PFS from diagnosis of ECS was 3 months (95% CI: 0–10).

3.5 | Safety and tolerability of adrenostatic treatment

Treatment-emergent adverse events (TEAE) of adrenostatic treatment are shown in Table 3. Two patients with adrenostatic treatment discontinued treatment due to TEAEs (renal failure and nausea/vomiting). The most frequently reported drug-related TEAEs were elevated liver function tests (4, n = 8) and infections (2, n = 8) for example, abdominal abscess and sepsis.

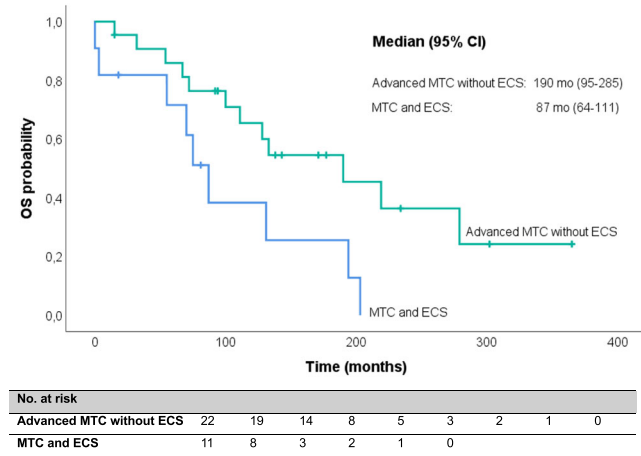


FIGURE 1 OS probability from the first diagnosis of MTC in patients with concomitant ECS compared to patients with advanced MTC without ECS matched by sex, age at MTC diagnosis (± 5 years), tumour stage and calcitonin doubling time. CI, confidence interval; ECS, ectopic Cushing's syndrome; MTC, medullary thyroid cancer; OS, overall survival [Color figure can be viewed at wileyonlinelibrary.com]

3.6 | Case studies: Tumour-specific therapy with MKI

Targeted therapies with vandetanib and cabozantinib as well as RET-inhibitors (selpercatinib and pralsetinib) were administered in one (9%) patient to resolve ECS and in two patients after resolution of ECS. These cases will be presented in more detail.

3.7 | Case 1

A 61-year-old female patient with advanced sporadic MTC presented for follow-up and showed calcitonin of 14.855 pg/ml (reference interval: 0–10) and CEA of 151 $\mu\text{g/L}$ (reference interval: 0.2–3.4). Random cortisol was 25.5 $\mu\text{g/dl}$ (reference interval: 5–25), ACTH was 96.5 ng/L (reference interval: 0–46) and 24-h urinary cortisol was 139 $\mu\text{g/day}$ (reference interval: 8–70). Midnight salivary cortisol was 2.3 $\mu\text{g/dl}$ (reference interval: 0–0.15) and serum cortisol did not suppress after low-dose dexamethasone suppression. Due to PD and metachronous ECS, treatment with vandetanib 300 mg/day was initiated. The first follow-up revealed stable disease (SD), calcitonin of 5685 pg/ml and control of hypercortisolism (serum morning cortisol 17 $\mu\text{g/dl}$, plasma ACTH not obtainable). After 8 months of vandetanib, treatment was switched to cabozantinib. Cortisol and ACTH levels remained unchanged (serum morning cortisol 11 $\mu\text{g/dl}$, ACTH 58 ng/L), and midnight salivary cortisol was in the normal range at 0.05 $\mu\text{g/dl}$ indicating control of ECS with both vandetanib and cabozantinib.

3.8 | Case 2

A 37-year-old male patient with sporadic RETM918T mutant MTC and previous peptide receptor radionuclide therapy with ^{177}Lu -DOTATATE after positive somatostatin receptor PET as well as MKI therapy with cabozantinib, vandetanib and nintedanib in a Phase 2 study developed lethargy, weight gain, peripheral oedema, muscle weakness and hypokalemia 2 years after MTC diagnosis. The 24-h urinary-free cortisol was extremely elevated at 10.331 $\mu\text{g/day}$ (reference interval: 8–70), morning cortisol was 49 $\mu\text{g/dl}$ (reference interval: 5–25) and ACTH was increased to 183 ng/L (reference interval: 0–46). Low-dose dexamethasone suppression testing failed to suppress cortisol production (serum cortisol after dexamethasone 47 $\mu\text{g/dl}$). Metyrapone therapy was initiated for bridging to BADX, which resulted in complete resolution of CS. One year later, selpercatinib was started as part of a clinical trial. Treatment duration was 9 months; the best radiographic response was partial remission and PFS was 4 months. The patient did not experience recurrence of hypercortisolism.

3.9 | Case 3

A 62-year-old male patient with advanced sporadic MTC presented 10 months after initial diagnosis with weight gain, easy bruising and skin atrophy. Calcitonin was 2460 pg/ml (reference interval: 0–10) and CEA 944 $\mu\text{g/L}$ (reference interval: 0.2–3.4), serum potassium was 3.3 mmol/L (reference interval: 3.5–5.1), random cortisol 223 $\mu\text{g/L}$ (reference interval: 48–195) and ACTH 131 ng/L (reference interval: 7–63). ECS was treated with mitotane and hydrocortisone replacement. Biochemical control of hypercortisolism was achieved within 2 months (random cortisol of 21 $\mu\text{g/L}$, ACTH of 60 pg/ml, potassium 4.2 mmol/L). Treatment had to be withdrawn due to drug intolerance (nausea, vomiting and elevated creatinine). BADX resulted in the complete resolution of symptoms of CS, without further recurrence of hypercortisolism. Almost 3 years later, treatment with vandetanib 200 mg/day was started due to PD. Imaging showed a response of liver and cervical lymph node metastases, calcitonin dropped from 14,078 to 666 pg/ml and ACTH from 215 to 42 pg/ml, suggesting response of ECS to vandetanib treatment.

4 | DISCUSSION

Here, we describe a cohort of patients with ECS due to MTC. The association of MTC and ECS is extremely rare and relevant data are limited to mostly case studies. Four patients out of this series with ECS were reported from a single centre with overall 673 MTC patients revealing a prevalence of ECS in MTC of 0.6%.⁹ While with 11 patients our study is comparable in size to others conducted on this topic, an advantage is a relatively recent accrual and the use of contemporary treatment options both for MTC and CS and availability of germline or somatic RET testing results. In addition, we

were able to compare the prognosis of MTC with ECS to matched controls from a large multi-centre registry. Our study shows that ECS occurs in advanced stage MTC and is associated with a poor prognosis. Based on recently published data and three cases from our cohort, it is to be expected that targeted treatment options will be a treatment option in patients with ECS secondary to *RET* mutant MTC.

More than 60 patient cases of CS due to MTC have been described in the literature. Most commonly, the diagnosis of MTC precedes the diagnosis of ECS.¹² In our cohort, the median time between initial diagnosis and diagnosis of ECS was 29 months and only 1 in 11 patients with MTC presented first with the ectopic cause of ACTH excess. Therefore, it is likely that most tumours acquire the ability to produce CRH/ACTH during the course of the disease, with a maximum time of 16 years in our cohort.

We found clinical characteristics, course, treatment and outcome to be comparable with published data sets with some remarkable differences. The mean age of 59 years is higher than in previous reports,^{12,16} however, the proportion of patients affected by a hereditary form of MTC is low and in accordance with previous reports.^{12,17,18} The high proportion of lymph node metastases at diagnosis is identical to the data from Barbosa et al.,¹² but the frequency of liver and lung metastases is even higher in this study than reported in the literature.¹⁸ All cases in our series exhibit aggressive biological characteristics as indicated by the advanced tumour stage at diagnosis and presence of distant metastases. Median CDT that is well established as an independent predictor of recurrence and survival^{19–21} was <1 year in all cases before ECS diagnosis confirming the aggressive course of the disease in these patients.

The most common clinical symptoms of glucocorticoid excess in our cohort (proximal muscle weakness, diabetes mellitus, cushingoid appearance) are in line with published data.^{22,23} Importantly, hypokalemia was present at diagnosis in a large proportion of patients—as frequently encountered in ECS—indicating the severity of hypercortisolism.^{24,25} Patients with a rapid disease progression after diagnosis of ECS (time between ECS diagnosis and death <12 months) did not present with cushingoid appearance presumably due to the rapid onset of intense hypercortisolism and concomitant progressive MTC. A clue to the diagnosis in these most severe cases of ECS is low potassium levels.

Establishing a diagnosis can be challenging clinically and is therefore based on the presence of hypercortisolism (with elevated or inappropriately normal ACTH levels) without adequate suppression after high-dose dexamethasone, the absence of pituitary tumour, and the parallel progression of MTC and CS. Nevertheless, CS may also remain unrecognized in patients even in endocrine expert centres given the atypical clinical presentation due to underlying malignant disease. Clinical suspicion of CS was confirmed in all patients by biochemical evidence of cortisol excess and unsuppressed ACTH. Nevertheless, the complete workup of ACTH-dependent CS that includes CRH testing²⁶ and IPSS was clinically considered dispensable in all patients in line with a consistent clinical picture in the context of advanced MTC. Beyond ectopic production of ACTH, ectopic production of CRH or cosecretion of CRH/ACTH cannot be ruled out in

our cohort, which is however exceedingly rare. Furthermore, it must be noted, that ectopic CRH/ACTH secretion of different origins cannot be fully excluded and in all cases with MEN2, concomitant Cushing's disease and ACTH cosecretion of pheochromocytoma cannot be ruled out.

Different from other causes of ECS, such as typical carcinoid and small cell lung cancer, surgical removal of the ectopic CRH/ACTH source (aetiologic surgery) is rarely possible in MTC due to advanced disease. BADX has been demonstrated to be safe in ECS.²⁷ In line with this, BADX was performed in four out of eight patients. No patient experienced an adrenal crisis. Nevertheless, it must be noted that different from other causes of ECS the prognosis of underlying disease in MTC is generally rather poor. Three patients did not receive any treatment of cortisol excess due to diagnosis of ECS at an advanced disease stage in a palliative care setting.

Outcome data showed a median PFS from diagnosis of ECS of 3 months and median OS of 14 months. Median OS from the initial diagnosis of MTC was 87 months. A matched cohort of patients with advanced MTC without ECS receiving MKI treatment with vandetanib and/or cabozantinib due to PD from a large multicentre registry showed a longer OS of 190 months.²⁸ This result supports the assumption that the outcome of MTC patients is further worsened in the presence of the paraneoplastic syndrome. Furthermore, it is noteworthy that the difference is even significant compared to patients with advanced MTC and PD. Causes of death were related to PD in four patients. In four patients, PD as well as complications and comorbidities of hypercortisolism were associated with death. The fact that all patients showed PD emphasizes the aggressiveness of the underlying tumour disease.

Published data confirm that the manifestation of ECS represents a poor prognosis with a mortality rate of up to 80% and survival no longer than 12.8 months after diagnosis of CS in the pre-MKI era cohort of Barbosa et al.¹² Very recent data highlight high mortality of up to 59% in a cohort of patients with active CS caused by malignancy.²⁵

Molecularly targeted therapies such as MKIs have profoundly changed the treatment landscape in advanced MTC. Vandetanib and cabozantinib have been approved by the United States Food and Drug Administration and the European Medicines Agency for patients with significant tumour burden, symptomatic and/or progressive metastatic disease.²⁹ In 2013, in a first published correspondence in the *New England Journal of Medicine*, vandetanib was shown to reverse ECS in a patient with MTC.³⁰ Further case reports and small case series followed, showing control of ACTH excess in adolescent and adult populations (Table 4).^{31–34} Beyond approved MKIs for advanced MTC, the usage of sorafenib and sunitinib have been described in further case reports on ECS in MTC.^{35–37} Recently, a first case was reported as an abstract, demonstrating a highly selective *RET* inhibitor therapy with selpercatinib to induce a total remission of ECS secondary to advanced *RET*-mutated MTC.³⁸ Another case report from Ireland showed a dramatic clinical and biochemical response to selpercatinib despite acquired resistance to vandetanib after 18 months of treatment in a patient with somatic *RET*M918T mutation.³³ Here, treatment with vandetanib in one patient was

TABLE 4 Reported cases of MTC and ECS treated with MKI

Authors	Year of publication	Country of origin	Treatment of ECS	Positive response to MKI treatment reported
Case reports				
Baudry et al., <i>N Engl J Med</i> ³⁰	2013	France	Metyrapone, mitotane, somatostatin analogues, ketoconazole, vandetanib	Yes
Barroso-Sousa et al., <i>Thyroid</i> ³⁵	2014	Brazil	Sorafenib	Yes
Nella et al., <i>J Clin Endocrinol Metab</i> ³¹	2014	US, Brazilian adolescent	Vandetanib	Yes
Hammami et al., <i>BMC Cancer</i> ³⁶	2015	Saudi Arabia	Sorafenib	Yes, without measurable reduction in cortisol concentration
Marques et al., <i>Endocrine</i> ³⁷	2015	Portugal	Sunitinib	Yes
Pitoia et al., <i>Arch Endocrinol Metab</i> ³²	2015	Argentina	Vandetanib	Yes
Matheny et al., <i>J Investig Med High Impact Case Rep</i> ³⁹	2016	US	Ketoconazole, mifepristone, etomidate, vandetanib, BADX	No
Paepegaey et al., <i>Thyroid</i> ⁴⁰	2017	France	Vandetanib	Yes
Agosto et al., <i>Thyroid</i> ³⁸	2019	US	Metyrapone, selpercatinib	Yes
Forde et al., <i>Endocrinol Diabetes Case Rep</i> ³³	2021	Ireland	Metyrapone, octreotide, LAR vandetanib, cabozantinib, selpercatinib	Yes
Case series				
Wijewardene et al., <i>Endocrinol Diabetes Metab Case Rep</i> ³⁴	2017	Australia	1. Case: vandetanib, ketoconazole, mitotane 2. Case: ketoconazole	1. Case: no 3. Case: no
This series			1. Case: vandetanib, cabozantinib 2. Case: metyrapone, BADX, selpercatinib, pralsetinib 3. Case: ketoconazole, vandetanib	1. Case: yes 2. Case: prior BADX, unknown 3. Case: prior BADX, yes

Abbreviations: BADX, bilateral adrenalectomy; ECS, ectopic Cushing's syndrome; MKI, multityrosine kinase inhibitor; MTC, medullary thyroid cancer.

effective in the management of ECS and resulted in clinical and biochemical control of ECS with a morphological tumour response of SD, as described in Case 1. Even if Case 3 received BADX before treatment with vandetanib, MKI treatment induced a remarkable reduction of ACTH. This is in accordance with recently published data on vandetanib in MTC patients with ECS showing a clinical and biochemical improvement of ECS after MKI treatment with vandetanib.^{30,31,34,39,40} Based on these case studies and the results of our retrospective analysis, targeted treatment with MKI such as vandetanib may be a beneficial treatment option in neuroendocrine tumour-related ECS, most likely due to a direct antisecretory action on neoplastic cells, which may be independent of its antitumoral effect.³⁰ First case reports also suggest a reversal of CS and a sustained tumour burden control with the RET inhibitor selpercatinib.^{33,38}

Our study of 11 MTC patients with ECS treated at four specialized centres has some limitations: missing data due to its retrospective nature, lack of complete diagnostic workup as described above, lack of systematic follow-up, heterogeneity of patient management and the evaluation of imaging findings by different radiologists.

5 | CONCLUSION

The clinical phenotype of ECS in MTC is highly variable and the typical clinical picture of CS is often lacking due to rapid onset and underlying malignant disease. Nevertheless, profound hypokalemia and the onset of proximal muscle weakness and/or diabetes mellitus in patients with MTC should raise suspicion for hypercortisolism. ECS

occurs in advanced stage MTC and is associated with a poor prognosis. Adrenostatic treatment and BADX were effective systemic treatment options in our cohort. Furthermore, in one case, MKI treatment succeeded in the complete remission of hypercortisolism and sustained tumour control. MKIs might therefore be considered as an alternative to BADX.

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CONFLICT OF INTERESTS

Viktoria F. Koehler has received honoraria for lectures and travel expenses from Novartis and Sanofi. Karin Frank-Raue and Friedhelm Raue received honoraria for lectures from Lilly and Merck. Emanuel Christ has received honoraria for advisory boards and lectures from Novartis and HRA. Christine Spitzweg has received honoraria for advisory boards and lectures from Ipsen, Lilly, Bayer, Eisai, Genzyme. Matthias Kroiss has received institutional research support from Ipsen, Loxo Oncology and Lilly, travel support from Eisai, Ipsen, HRA Pharma, MCI Germany and Lilly, honoraria for lectures from Bristol-Myers Squibb, Eisai, Lilly, and MSD and consultancy honoraria from Lilly. Carmina T. Fuss, Christina M. Berr, Eva Hoster, Matthias Hepprich, Thomas Pusch and Martin Reincke have no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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