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ORIGINAL ARTICLE

Hypokalaemia and hypercortisolaemia at diagnosis are negative prognostic factors: a retrospective analysis of the medical management of ectopic Cushing syndrome

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Background: Ectopic Cushing syndrome (ECS), related to neuroendocrine neoplasms (NENs), is a rare condition with high morbidity and mortality. We hypothesised that both the severity of hypercortisolaemia and hypokalaemia correlates with prognosis.

Materials and methods: Fifty-five patients with ECS (37 females), with a mean age of 54 ± 14 (standard deviation) years were identified in our database for further analysis of clinical parameters, biochemical data, symptomatic treatment and outcome.

Results: Twenty-eight patients had bronchial, 16 pancreatic, 4 thymic and 1 a rectal NEN. In six patients, the primary tumour was unknown. The proliferation index, Ki-67, was ≤20% in 31 patients and hypokalaemia correlated negatively with Ki-67 ($P = 0.043$). Severe hypokalaemia at diagnosis (<2.5 mmol/l) was found in 50% of the patients. Hypokalaemia and high doses of potassium substitution were associated with shorter overall survival ($P = 0.009$ and $P = 0.019$, respectively). However, only severe hypercortisolaemia remained an independent negative factor for survival in multivariate analysis ($P = 0.042$). Potassium substitution was required in 87% of patients and the dose was positively correlated to baseline hormone levels including urinary free cortisol ($P < 0.001$), s-cortisol ($P < 0.001$) and adrenocortical hormone (ACTH) ($P = 0.016$). Steroidogenesis inhibitors (SIs) were used as initial treatment in 46 patients to improve symptoms. However, within 1 month, 17 proceeded to bilateral adrenalectomy and 3 died.

Conclusions: We conclude that only hypercortisolaemia was independently prognostic for shorter survival. Furthermore, we suggest that hypercortisolaemia, especially in combination with severe hypokalaemia (<2.5 mmol/l), indicates an acute life-threatening situation. For these patients, immediate actions should be considered to reduce cortisol levels and bilateral adrenalectomy should be discussed upfront.

Key words: ectopic Cushing syndrome, neuroendocrine neoplasia, ACTH, hypokalaemia, steroidogenesis inhibitors

INTRODUCTION

Cushing syndrome (CS) with an estimated incidence of 0.2-5.0 per million people per year[1] is a rare medical condition characterised by a number of severe metabolic disturbances due to glucocorticoid excess. The majority of adrenocortical hormone (ACTH)-dependent CS is caused by ACTH-secreting pituitary adenomas while ectopic CS (ECS), caused by ACTH or corticotropin-releasing hormone secretion by non-pituitary tumours, represents only 5%-10% of CS.[1,2] Although the two most frequent sources of ECS are small-cell lung cancer (3.3%-50%) and neuroendocrine neoplasms (NENs) of various origin (2%-42%), other non-neuroendocrine tumours (NETs) can cause ECS (≤5%) in rare cases.[2] In up to one-third of patients with ECS, the source of ACTH secretion is never found (defined as occult ECS) or found after decades of follow-up.[2]

Clinical management of ECS is difficult and may include the need for intensive care during prolonged periods of time. Life-threatening complications such as opportunistic infections, thromboembolism, hypokalaemia and hypertensive crises have a much higher prevalence in ECS compared with CS of other origins and are the main reasons for hospitalisation.[3] In conditions of extremely high cortisol levels, not all available cortisol can be inactivated to cortisone. As a result, cortisol binds to aldosterone receptors causing peripheral effects simulating mineralocorticoid

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hyperproduction (hypokalaemia and metabolic alkalosis). In ECS, hypokalaemic alkalosis has been reported in up to 95%-100% of cases, in contrast to <10% in other forms of CS.[4] Due to this, ECS should be considered as an endocrine emergency requiring an 'emergency response'.[5] Immediate symptomatic treatment is often needed including per oral and/or intravenous potassium substitution, insulin, anticoagulation treatment and antibiotics.

Since tumours of very different malignant potential can cause ECS, it is crucial to understand if the hormone- or tumour-related risk is dominating before the therapeutic strategy is decided. The Endocrine Society guidelines recommend urgent treatment (within 24-72 h) of the hypercortisolism if life-threatening complications related to the CS such as severe infections, pulmonary thromboembolism, cardiovascular complications or acute psychosis are present.[6] Secretion of multiple hormones has also been identified as a bad prognostic factor and should lead to rapid clinical intervention.[7] If radical surgery of an ACTH-producing tumour is not possible, steroidogenesis inhibitors (SIs), such as ketoconazole or metyrapone, are recommended as the primary treatment for ECS in patients with occult or metastatic ECS, followed by bilateral adrenalectomy (BA) if necessary.[6] Effective reduction of cortisol levels and thus improvement of the patient's general condition is essential in order to start antitumour treatment.

Due to the rarity of the condition, large retrospective or prospective studies are lacking. We aimed to describe and analyse the medical management of hypokalaemia and hypercortisolaemia in ECS. Our hypothesis was that hypercortisolaemia, hypokalaemia and the need for potassium supplementation are negative prognostic factors in ECS, and that these parameters affect overall morbidity and mortality in this rare condition.

MATERIALS AND METHODS

Patients and data

A retrospective cohort of 62 patients with biochemically and radiologically confirmed ECS was identified from a database including all patients with NENs treated at the Department of Endocrine Oncology, Uppsala University Hospital between 1984 and 2023. Patients with occult ECS ($n = 5$) and with ACTH-producing prostate cancer ($n = 2$) were excluded and 55 patients' medical records were further analysed.

The ECS cohort was divided into four subgroups by using either the latest World Health Organization classification of digestive NENs from 2019,[8] or by proliferation index (Ki-67) and tumour morphology for NENs of other origin than digestive (lung or thymus) and a dedicated pathologist at the Uppsala University Hospital had reviewed all tumour specimens. These four groups included well-differentiated tumours G1 NET or Ki-67 <3%; G2 NET or Ki-67 3%-20%; G3 NET or Ki-67 >20% and poorly differentiated tumours: neuroendocrine cancer or Ki-67 >20%. Finally, there was a group of patients with a tumour defined as NEN but with no Ki-67 staining available. No new histopathological examination was carried out.

All procedures carried out in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the local ethics committee, Regionala etikprövningsnämnden (EPN), in Uppsala, Sweden. The need for informed consent was waived by the local ethics committee.

Biochemical data and treatment

Basic clinicopathological parameters including sex, age and tumour diagnosis, biochemical and hormone data, as well as data regarding symptomatic treatment of ECS and treatment outcome were collected. We analysed management of hypokalaemia, type and dose of SI used, and how SI influenced hormone levels.

Potassium and glucose levels (mmol/l) were collected at baseline (lowest for potassium and highest for glucose) and either before surgery (BA or radical resection of the primary tumour) or simultaneously with hormone analyses when evaluating SI therapy. Hyperglycaemia was defined as fasting glucose ≥7.0 mmol/l and hypokalaemia as potassium <3.5 mmol/l: 3-3.4 mmol/l as mild, 2.5-2.9 mmol/l as moderate and <2.5 mmol/l as severe hypokalaemia.

Hormone levels [ACTH, 24-h urine free cortisol (UFC) and morning s-cortisol] were measured at baseline and at the first follow-up (not earlier than after 1 week) after initiation of SI or somatostatin analogue (SSA) treatment. Because the study was retrospective, covering several decades, the upper hormone reference level varied slightly and therefore multiples of upper limit of normal (ULN) are used to describe hormone levels.

When the efficacy of SI treatment was analysed, patients with cyclic ECS and those receiving chemotherapy in parallel with SI were excluded. Furthermore, only patients for whom two measurements of hormonal levels were available were included in the analyses.

As this study focuses on medical management of ECS, both time from diagnosis of the NEN as well as time from diagnosis of ECS were used when calculating overall survival (OS). When analysing the cause of death, patients were divided into two groups, depending on whether they had undergone BA or not.

Statistical analysis

Normally distributed data were reported as means ± standard deviation (SD). Differences in means between groups were evaluated using *t*-test or one-way analysis of variance (ANOVA). Data with skewed distribution and/or outliers were described as medians, accompanied by the 25th-75th percentile ranges (Q1-Q3) and analysed by non-parametric tests. Correlations were estimated using Spearman's correlation test. Survival data were obtained by the Kaplan—Meier analysis and between-group differences were evaluated using the log-tank test. Cox proportional regression was carried out for the estimation of

Table 1. Baseline characteristics of the study population

Variable	Values	$n = 55$[a]	%
Sex	Female	37	67
	Male	18	33
Age at diagnosis of tumour/ECS (years)	<40	11/10	20/18
	41-70	35/36	64/66
	>70	9/9	16/16
Primary tumour localisation	Bronchus (TC = 3, AC = 15, NEC[b] = 5, N/D = 5)	28	51
	Thymus (AC = 4)	4	7
	Pancreas (G2 NET = 10, G3 NET = 3, N/D = 3)	16	29
	Rectum (NEC = 1)	1	2
	CUP	6	11
Histopathological characteristics/groups[c]	G1 NET or Ki-67 <3%	7	13
	G2 NET or Ki-67 3%-20%	24	44
	G3 NET or Ki-67 >20% (well differentiated)	6	11
	NEC or Ki-67 >20% (poorly differentiated)	8	14
	Unknown	10	18
Metastases at diagnosis of ECS	Liver	35	64
	Lymph nodes	25	45
	Bones	9	16
	Lungs	9	16
	Others (adrenal/subcutaneous/ brain/parotid gland)	9 (4/2/2/1)	16
	No metastases	11	20

AC, atypical carcinoid; CUP, cancer of unknown primary; ECS, ectopic Cushing syndrome; N/D, not defined; NEC, neuroendocrine cancer; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; TC, typical carcinoid; WHO, World Health Organization.

[a] $n = 55$ was the total number of the patients in the ECS cohort.

[b] Small cell lung carcinoma excluded.

[c] Regarding histopathological characteristics, the cohort was divided into four subgroups by using both the latest WHO classification of digestive tumours (G = grade), proliferation index (Ki-67) and tumour morphology.

hazard ratios (HRs) and confidence intervals (CIs). The chi-square test was used for testing relationships between categorical variables. The defined event was death from any cause. OS was defined as time from diagnosis until the date of death, or if event was not found, censored at date of last observation, 1 March 2022. The level of statistical significance was set to 0.05. All statistical analyses were carried out using IBM SPSS statistical software (v28, IBM, Armonk, NY).

RESULTS

Study patients

Fifty-five patients with ECS were identified including 37 females (67%) and 18 males (33%). Mean age at diagnosis of tumour was 54 years ± 14 SD (min-max: 15-77 years) and at diagnosis of ECS was 55 years ± 15 SD (18-80 years). A majority of the patients had bronchial ($n = 28$) or pancreatic NENs ($n = 16$), followed by thymic ($n = 4$), rectal ($n = 1$) and metastasised NENs with unknown primary localisation (CUP) ($n = 6$). Thirty-one patients (56%) were diagnosed simultaneously with tumour and ECS. Nineteen patients (35%) had their tumour diagnosis first while five patients (9%) were diagnosed with ECS before the primary tumour was localised. The median time (min-max) between diagnosis of tumour before ECS was 36 months (2-220 months) and the median time between ECS and a later tumour diagnosis was 51 months (2-396 months).

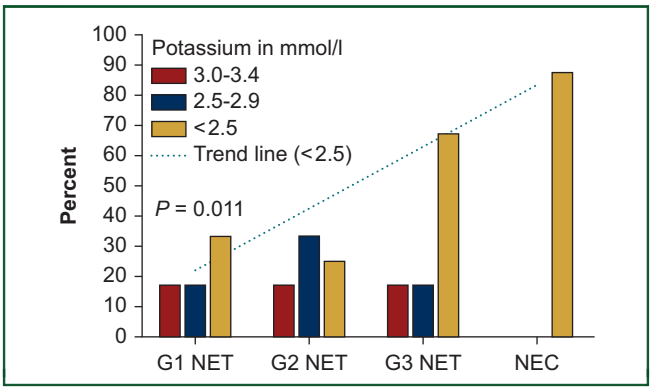

Figure 1. Bar chart for patients with ectopic Cushing's syndrome (ECS) showing distribution of patients in percent within different tumour proliferation groups depending on potassium levels.
NEC, neuroendocrine cancer; NET, neuroendocrine tumour.

Four patients had cyclic ACTH secretion: two patients with pancreatic NEN, one with thymic NEN and one with CUP. Forty-four patients (80%) had metastatic disease at diagnosis of ECS with predominance of liver metastases. Nineteen patients (43%) had one metastatic location while 10 patients (23%) and 15 patients (34%) had metastases in 2 or ≥3 locations, respectively. A majority of the patients had G1 ($n = 7$) and G2 ($n = 24$) NETs. Staining for Ki-67 index was not carried out in 10 cases who were diagnosed with ECS before 2000. Basic characteristics of the cohort are presented in Table 1.

Median ACTH ($n = 50$) at baseline was 151 ng/l (range 105-296 ng/l), median UFC ($n = 52$) was 4910 nmol/24 h (range 2779-23108 nmol/24 h) and median s-cortisol ($n = 45$) was 1380 nmol/l (range 891-2104 nmol/l). UFC was 1-2 × ULN in 5 patients, 3-10 × ULN in 13 patients and >10 × ULN in 34 patients. Hyperglycaemia was seen in 75% and hypokalaemia in 79% of patients at diagnosis: mild hypokalaemia was found in 9 patients, moderate in 12 patients and severe in 21 patients at diagnosis. In a few cases, potassium was within the reference range at diagnosis and treatment-requiring hypokalaemia developed subsequently during progression of ECS/tumour disease.

Management of hypokalaemia

Mean potassium ($n = 53$) at baseline in the whole cohort was 2.7 ± 0.7 mmol/l (1.6-4.1 mmol/l). Mean potassium level among patients with hypokalaemia at baseline was 2.5 mmol/l. Potassium levels were negatively correlated to ACTH ($\rho = -0.3$, $P = 0.0130$), UFC ($\rho = -0.5$, $P < 0.001$) and s-cortisol ($\rho = -0.6$, $P < 0.001$) levels at diagnosis. Additionally, we observed that among patients with poorly differentiated tumours, there were fewer cases of mild to moderate hypokalaemia than severe hypokalaemia ($P = 0.011$; see Figure 1).

In 48 patients, potassium substitution treatment was needed during the course of disease: 25 were given per oral treatment only, while 23 also needed intravenous potassium. The dose of intravenous potassium substitution was known in only 12 cases due to reduced access to and incomplete documentation in older medical records. Mean

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Table 2. Hormone levels, potassium substitution and spironolactone therapy at diagnosis of ECS

Potassium substitution				
Hormones	No K substitution	K p.o. only	K p.o. and i.v.	*P* value
ACTH	113 (74-139)	137 (99-299)	250 (133-424)	0.185
UFC	1951 (297-4657)	4234 (2616-7115)	19 105 (4815-44 685)	0.003[a]
s-cortisol	704 (607-934)	1201 (841-1776)	2027 (1350-3662)	0.006[a]
Dose of potassium p.o.				
	1-2500 mg	2501-4500 mg	4501-9000 mg	9001-18 000 mg	*P* value
ACTH	122 (54-473)	178 (120-310)	236 (200-468)	250 (86-771)	0.245
UFC	3777 (2616-7115)	4260 (1656-5900)	6510 (5180-36 960)	39 000 (26 511-79 452)	<0.001[a]
s-cortisol	1220 (797-1869)	1268 (895-2167)	1850 (1263-3253)	2054 (1600-3956)	0.010[a]
Dose of spironolactone				
	No treatment	25-75 mg	100-175 mg	200-1000 mg	*P* value
ACTH	116 (75-143)	266 (153-455)	159 (55-272)	231 (209-756)	0.036[a]
UFC	2711 (1224-5030)	6009 (4275-30 033)	9705 (4600-56 465)	7061 (4166-36 246)	0.006[a]
s-cortisol	1067 (785-1600)	1305 (665-3161)	2000 (1201-3500)	1869 (1191-2407)	0.070[a]

ACTH, UFC and s-cortisol values represented as medians in ng/ml, nmol/24 h and nmol/l, respectively, accompanied by the 25th-75th percentile ranges.
ACTH, adrenocortical hormone; ECS, ectopic Cushing syndrome; i.v., intravenously; K, potassium; p.o. by mouth; UFC, 24-h urine free cortisol.
[a]Statistically significant ($P < 0.05$) value.

dose per 24 h of potassium was 5112 mg (0-18 000 mg) orally and 43 mmol (0-360 mmol) intravenously. Spironolactone was used in 34 patients in the following daily doses: 25-75 mg ($n = 14$), 100-175 mg ($n = 11$) and 200-1000 mg ($n = 8$). Patients who managed without potassium substitution had significantly lower levels of s-cortisol and UFC at ECS diagnosis compared with those who needed potassium substitution, and the highest median level was found in those who needed intravenous potassium treatment. We found a positive correlation between oral potassium dose and UFC ($\rho = 0.6$, $P < 0.001$), s-cortisol ($\rho = 0.5$, $P < 0.001$) and ACTH ($\rho = 0.3$, $P = 0.016$) levels at ECS diagnosis. Furthermore, we found a positive correlation between the dose of spironolactone and UFC ($\rho = 0.5$, $P < 0.001$), s-cortisol ($\rho = 0.4$, $P = 0.011$) and ACTH ($\rho = 0.3$, $P = 0.039$) levels. A summary of hormone levels at diagnosis of ECS, potassium substitution and spironolactone therapy is presented in Table 2 and Figure 2.

Ki-67 index correlated negatively with serum potassium levels ($\rho = -0.3$, $P = 0.043$) and positively with UFC levels ($\rho = 0.3$, $P = 0.042$) at baseline, and patients with well-differentiated NET G3 needed significantly higher doses of per-oral potassium substitution ($P < 0.001$), compared with those with lower Ki-67. This patient group also showed a tendency to have higher UFC at diagnosis (see Figure 3 and Table 3).

Management of hypercortisolaemia

BA was carried out in 35 patients in this cohort. The advantages and disadvantages of BA as treatment of ECS have been described previously.[9]

Forty-six patients were treated with SI in order to reduce cortisol levels, either as monotherapy or in different combinations. Ketoconazole was used most often ($n = 43$), followed by metyrapone ($n = 21$), mitotane ($n = 1$) and etomidate ($n = 1$). Eleven patients received two or more SI in parallel, most often the combination of ketoconazole and metyrapone ($n = 10$). Ketoconazole was used in the following daily doses: 400 mg ($n = 20$), 600-800 mg ($n = 12$) and ≥1000 mg ($n = 9$), where six patients received 1200 mg and one patient 1600 mg, with the median being 600 mg. Among patients receiving metyrapone, the median dose was 750 mg and the majority received 500-2000 mg daily ($n = 18$). However, three patients needed higher doses: 2250 mg ($n = 2$) and 3000 mg ($n = 1$), respectively. Ten patients received supplementary glucocorticoid treatment to avoid acute adrenal insufficiency during SI treatment: two were treated with ketoconazole or metyrapone as monotherapy and six with the combination of both. Two of these 10 patients had cyclic ECS.

Eleven patients (24%) experienced different side-effects during SI treatment, most frequently an elevation of liver enzymes in patients receiving ketoconazole ($n = 8$). SI was used for ≤1 month in 23 patients, for 2-6 months in 14 patients and for >6 months in 8 patients (duration not known in one case). Although there was a statistically significant reduction of UFC and cortisol levels during SI treatment (Table 4), the median level of UFC at the first follow-up after SI therapy initiation was still 2-3 × ULN. In 14 patients, the dose of potassium could be reduced during SI therapy.

Among the 22 patients who were treated with SI for ≤1 month, 17 proceeded with subacute BA because of uncontrolled ECS symptoms. Two patients were operated radically for their primary tumour and three died within 4 weeks from their ECS diagnosis. All three patients with early fatal outcome had NET G3 with severe hypokalaemia (1.9 mmol/l) and very high UFC at diagnosis (28 934-79 452 nmol/24 h). The group of patients who received short-term SI therapy had higher median UFC levels at baseline compared with the group who used SI for >1 month: 26 511 nmol/24 h (33 × ULN) versus 4520 nmol/24 h (6 × ULN; $P = 0.030$). However, there was no difference in s-cortisol or ACTH levels between the two groups.

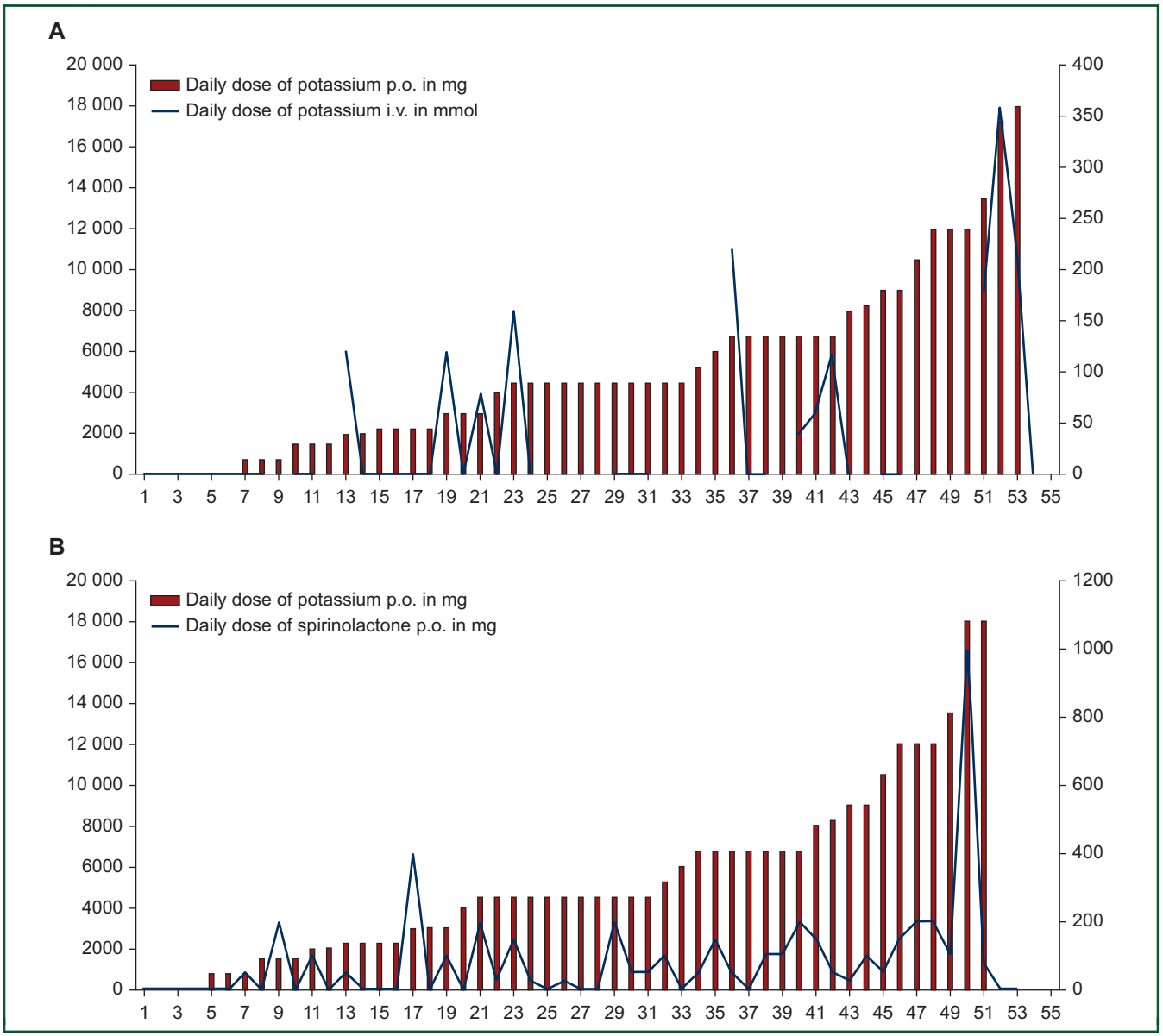

Figure 2. **Bar charts for patients with ectopic Cushing's syndrome (ECS) showing (A) dose of potassium substitution therapy in the cohort per patient both p/o and i/v and (B) dosage of spironolactone per patient.**

Nine patients (bronchial NEN $n = 4$, pancreatic NEN $n = 4$, CUP $n = 1$) were treated with SSA with the purpose of reducing ACTH and subsequently cortisol levels, and in seven patients either clinical or biochemical improvement of their ECS was obtained.

Four patients had cyclic ACTH secretion. Three were treated repeatedly with SI during the periods of hypercortisolaemia. However, it was very challenging to evaluate if the clinical and biochemical improvement was a result of the SI treatment or depended on a spontaneous reduction of ACTH secretion making it difficult to establish the efficacy of the SI treatment.

Survival

At the end of follow-up, 13 patients were still alive (bronchial NEN = 8, pancreatic NEN = 3, CUP = 2) with a median duration of follow-up of 155 months (range 15-340 months) while 42 patients had died. Causes of death were tumour progression with normal s-cortisol ($n = 21$; BA/no-BA = 20/1), tumour progression with elevated s-cortisol ($n = 6$; 0/6), complications due to elevated cortisol ($n = 7$; 4/3) and other non-tumour/ECS-related reasons ($n = 5$; 4/1). Cause of death was unknown in three patients.

Median OS from ECS diagnosis in the whole cohort was 26 months (95% CI 13-38 months), with a 5-year survival rate of 26%. A clear difference in OS was seen when comparing tumours with different proliferation index as demonstrated in Table 5. Potassium levels <2.5 mmol/l were correlated with shorter OS when compared with the group with higher potassium levels [12 months (95% CI 0-24 months) versus 39 months (95% CI 15-62 months), respectively, $P = 0.009$]. Furthermore, shorter OS was found in patients with higher Ki-67 ($P = 0.024$) and higher s-cortisol at diagnosis ($P = 0.004$). Severe hypercortisolaemia remained a statistically significant

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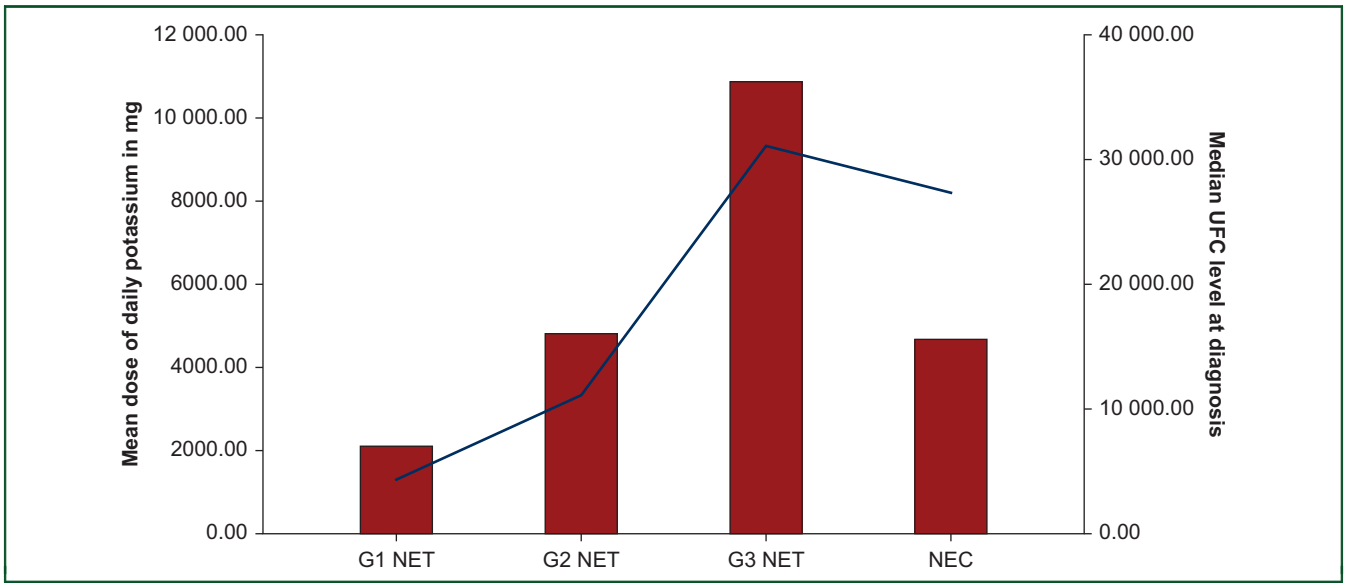

Figure 3. Bar chart demonstrating mean dose of potassium substitution orally and median 24 h-UFC levels at diagnosis, depending on histological differentiation of tumour.
NEC, neuroendocrine cancer; NET, neuroendocrine tumour; UFC, urine free cortisol.

independent negative factor for survival in multivariate Cox regression analysis (HR 2.4, 95% CI 1.0-5.8, $P = 0.042$) regardless of Ki-67 as demonstrated in Table 6. Patients who needed a combination of both oral and intravenous potassium substitution had shorter OS from diagnosis of ECS compared with those with per-oral treatment only (19 and 46 months respectively; HR 1.4, 95% CI 1.1-1.9, $P = 0.008$). Furthermore, the higher doses of per-oral potassium and spironolactone that was needed, the shorter OS was observed (HR 1.4, 95% CI 1.1-1.9, $P = 0.019$ and HR 2.0, 95% CI 1.5-2.9, $P < 0.001$, respectively), and this correlation was independent from UFC levels at diagnosis. Patients who received SI for only 1 month or less had a tendency towards shorter OS compared with the group with prolonged treatment [13 months (95% CI 0-28 months) versus 56 months (95% CI 32-80 months), respectively].

DISCUSSION

This study provides supporting evidence that ECS is a very difficult subtype of CS in terms of medical management. The severity of hypokalaemia is a clear negative prognostic factor and correlates with hypercortisolaemia. Severe hypercortisolaemia at diagnosis is an independent prognostic factor for shorter survival. Furthermore, hypercortisolaemia in combination with severe hypokalaemia indicates an urgent need for intervention to control ECS. In these cases, SI seem not be sufficient and we suggest that BA should be considered at an early stage.

In our cohort, hypokalaemia was present in 87% of patients at diagnosis and in 50% of the cases it was considered severe with potassium levels <2.5 mmol/l. In almost half of the cases, a combination of per-oral and intravenous treatment was needed to maintain serum potassium within a reasonable level. The mean potassium level in our cohort was 2.7 mmol/l, which is similar to the levels reported by Stachowska et al.[10] In our study, only a minority of patients managed without potassium substitution throughout the course of the disease. Importantly, ECS is only one of several possible causes of severe hypokalaemia associated with malignancy. In poorly differentiated NENs in particular, hypokalaemia may be multifactorial, depending not only on hypercortisolaemia but also on kidney and gastrointestinal losses of potassium related to chemotherapy (platinum) for example, or vomiting and diarrhoea.[11]

Table 3. Potassium and hormone levels at baseline related to tumour proliferation index

	Potassium	ACTH	UFC	s-cortisol
G1 Ki-67 <3%	3.0 (1.7-4.1) $n = 6$	139 (74-209) $n = 7$	4000 (482-8223) $n = 7$	1255 (610-2190) $n = 6$
G2 Ki-67 3%-20%	2.9 (1.7-4.0) $n = 24$	137 (59-236) $n = 23$	4520 (2709-8561) $n = 22$	1169 (801-2169) $n = 22$
G3 Ki-67 >20% well diff	2.3 (1.9-3.0) $n = 6$	252 (140-311) $n = 5$	19105 (5537-50 687) $n = 6$	1200 (926-3968) $n = 3$
NEC Ki-67 >20% poorly diff	2.2 (1.6-3.9) $n = 8$	208 (111-420) $n = 6$	6510 (2894-66 861) $n = 7$	1927 (1246-4673) $n = 6$
P value	0.039[a]	0.536	0.050[a]	0.451

Upper reference for ACTH 40-72 ng/l, for 24 h for UFC 230-372 nmol, for s-cortisol 540-800 nmol/l. Potassium represented in mmol/l (min-max). Hormone levels represented as medians accompanied by the 25th-75th percentile ranges.
ACTH, adrenocorticotropic hormone; diff, differentiated; G1, grade 1; G2, grade 2; G3, grade 3; NEC, neuroendocrine carcinoma; UFC, 24-h urine free cortisol.
[a]Statistically significant ($P < 0.05$) value.

Table 4. Median hormone levels before SI treatment and at first control

Hormones	Before SI	After SI	*P* value
UFC ($n = 25$)	4800 (2649-10 561)	1465 (421-2964)	<0.001[a]
s-cortisol ($n = 12$)	2077 (1277-3018)	926 (583-1273)	0.003[a]
Cyclic ECS and simultaneous cytostatic treatment excluded			
UFC ($n = 11$)	4500 (2683-8223)	1465 (445-2500)	0.003[a]
s-cortisol ($n = 5$)	3118 (1365-4090)	1095 (612-2160)	0.043[a]

ACTH, UFC and s-cortisol values represented as medians in ng/ml, nmol/24 h and nmol/l, respectively, accompanied by the 25th-75th percentile ranges. Patients with cyclic ECS were excluded.

ACTH, adrenocortical hormone; ECS, ectopic Cushing syndrome; SI, steroidogenesis inhibitors; UFC, 24-h urine free cortisol.

[a]Statistically significant ($P < 0.05$) value.

Although a majority of the patients had very high hormone levels at diagnosis, 10% of the patients in our cohort had UFC that was elevated <3 × ULN. This finding is in contradiction to the report of Lavoillotte et al. who could not find such low levels of UFC within their cohort of patients with ECS. They concluded that UFC levels can be used to discriminate between Cushing disease and ectopic ACTH secretion, a finding that we cannot confirm.[12]

Previous studies have described a negative correlation between potassium and hormone levels[7,13] and this was confirmed in our study. Furthermore, hypokalaemia has been shown to be a negative prognostic factor in ECS.[7,14] In our cohort, severe hypokalaemia, high doses of oral potassium substitution and spironolactone were correlated to shorter OS. According to drugs.com (https://www.drugs.com/dosage/potassium-chloride.html) the maximum daily dose of oral intake of potassium chloride should not exceed 200 mEq (15 000 mg): two patients in our cohort received 18 000 mg potassium orally in parallel with intravenous substitution. It is suggested that intravenous potassium administration should be used if the potassium level is <2.5 mmol and the recommended dose is 100 mmol/day with a maximum infusion rate of 20 mmol/h.[15] In critical cases you may infuse 40 mmol/h with continuous cardiac monitoring. Among the 12 patients with known dose of intravenous potassium substitution in our cohort, 8 needed a higher dose than 100 mmol/day, demonstrating the severity of hypokalaemia. Despite the high doses used, we did not record any cardiac arrhythmia or other side-effects due to the potassium treatment.

Although SI treatment decreased s-cortisol, the reduction in our cohort was not sufficient enough to reach normalised levels, and most patients proceeded to BA to improve their general condition. Yet, SI is recommended as the primary treatment in metastatic ECS[6] and was used in 84% of our patients. This is in contrast to the 37% reported in the ERCUSYN cohort[16] and 30% reported by Chen et al.[14] Although we observed significant reduction of cortisol during SI treatment, levels were still elevated: in only 26% of our patients we could reduce the potassium substitution following SI treatment and a majority still needed to proceed with BA. At the end of the follow-up half of the patients had died of progressive tumour disease with or without high cortisol levels, while hypercortisolaemia was confirmed as the direct cause of death in only 13% of patients.

Almost half of our patients were treated with SI for ≤1 month. They had significantly higher hormone levels at ECS diagnosis and had a tendency towards shorter OS compared with those receiving SI treatment for a longer period of time. This demonstrates that SI treatment is not sufficient to control ECS in many patients and they either fail to respond to treatment and die ($n = 3$) or need to proceed with BA to control the ECS ($n = 17$).

Although ketoconazole is effective in the treatment of CS, studies have shown normalisation of cortisol levels in only 44% of ECS patients.[6] The recommended maximum dosage of ketoconazole varies between 1200 mg[5,17] and 1600 mg/daily.[6] In our cohort, 16% of patients needed a daily dose of 1200 mg or higher which indicates a difficult-to-manage hypercortisolaemia. Metyrapone is the second most used SI with a recommended daily dose up to 6000 mg and has fast onset of action. However, it can worsen hypokalaemia by increasing mineralocorticoid precursors, and due to its rapid effect, there is a risk for acute adrenal insufficiency. Only three patients were treated with metyrapone as monotherapy and the maximum dose used was 3000 mg. If more than one SI was used, all but one patient were treated with ketoconazole first and metyrapone was added later either due to the unsatisfying effect of ketoconazole or side-effects preventing dose escalation. Thus, patients receiving metyrapone had as a group more severe metabolic disturbances and could therefore not tolerate the highest recommended doses of the drug. Ten patients received glucocorticoids in parallel with SI and eight of them were treated with metyrapone. One patient received etomidate which is the only SI available for intravenous use in intensive care units. The novel SI osilodrostat is the only SI that has been assessed in prospective randomised controlled trials.[18] Although the initial clinical trials focused on Cushing disease,[19,20] there are promising data on its efficacy for all types of endogenous CS[21,22] but none of our patients received this treatment.

High UFC levels at baseline as well as the highest doses of potassium substitution needed were observed in NET G3 patients suggesting that this group may have a more aggressive ECS compared with patients with lower proliferation rate. Similar data were reported in a Finnish cohort.[23]

Table 5. Survival and follow-up time in ECS depending on proliferation index Ki-67 and origin of the primary tumour

Variable	*n*	Follow-up months/min-max		Median OS (months)[a]		HR (95% CI)		*P* value		5-year survival (%)	
		T	ECS	T	ECS	T	ECS	T	ECS	T	ECS
Whole cohort	55	1-365	1-482	47	26	N/A		N/A		43	26
G1 Ki-67 <3%	7	4-338	4-482	242	N/D[a]	1.8 (1.2-2.8)	1.6 (1.1-2.3)	0.003[b]	0.009[b]	45	51
G2 Ki-67 3%-20%	24	2-216	2-222	55	46					42	25
G3 Ki-67 >20% well diff	6	12-163	3-81	95	7					44	16
NEC Ki-67 >20% poorly diff	8	1-60	1-61	4	4					12	12
Bronchial NEN	28	1-369	1-482	44	24	1.1 (0.8-1.6)	1.1 (0.8-1.5)	0.474	0.449	43	29
Thymic NEN	4	47-96	23-96	82	44					75	50
Pancreatic NEN	16	2-216	2-222	49	46					41	20
Rectal NEN	1	15	13	15	13					0	0
CUP	6	1-96	1-61	4	4					33	25

Survival data represented from diagnosis of tumour (T) and from diagnosis of ECS.
CI, confidence interval; CUP, cancer of unknown primary; diff, differentiated; ECS, ectopic Cushing syndrome; HR, hazard ratio; N/A, not applicable; N/D, not defined; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; OS, overall survival; T, tumour.
[a]Median survival time is not defined because percent survival at the end of the follow-up exceeds 50%.
[b]Statistically significant ($P < 0.05$) value.

Table 6. Univariate and multivariate analysis of prognostic factors for survival in ectopic Cushing syndrome

Variable		HR (95% CI)	*P* value
Univariate analysis			
Age (years)	>54 versus ≤54	1.5 (0.8-3.0)	0.191
Sex	Male versus female	1.0 (0.6-2.0)	0.840
Ki-67	>55% versus 20%-55% versus <20%	2.0 (0.9-4.0)	0.024[a]
Serum cortisol nmol/l	>1380 versus ≤1380	2.8 (1.4-5.8)	0.004[a]
ACTH ng/ml	>151 versus ≤151	1.2 (0.6-2.3)	0.568
UFC nmol/24 h	>4910 versus ≤4910	1.1 (0.6-2.0)	0.704
Potassium mmol/l	≥2.5 versus <2.5	0.4 (0.2-0.8)	0.009[a]
Multivariate analysis			
Serum cortisol nmol/l Ki-67	>1380 versus ≤1380 >55% versus 20%-55% versus <20%	2.8 (1.2-6.4) 1.5 (0.9-2.6)	0.012[a] 0.113
Serum cortisol nmol/l Potassium mmol/l	>1380 versus ≤1380 ≥2.5 versus <2.5	2.8 (1.0-5.0) 0.5 (0.1-1.2)	0.037[a] 0.137
Serum cortisol nmol/l Potassium mmol/l Ki-67	>1380 versus ≤1380 ≥2.5 versus <2.5 >55% versus 20%-55% versus <20%	2.4 (1.0-5.8) 0.6 (0.2-1.7) 1.3 (0.7-2.5)	0.042[a] 0.390 0.343

Hazard ratio (HR) and 95% confidence intervals (CIs) obtained from Cox regression models.
ACTH, UFC and cortisol are divided into two groups (low versus high) by using the median hormone level as cut-off.
ACTH, adrenocortical hormone; UFC, urine free cortisol.
[a]Statistically significant ($P < 0.05$) value.

There are a few smaller studies and case reports on the benefit of SSA in ECS.[24–27] In our cohort, seven out of nine patients had documented clinical and/or biochemical improvement of ECS during SSA treatment. However, it is not possible to confirm the response being solely an effect of SSA since most of the patients received SI and/or antitumour treatment in parallel.

This study has three main limitations. Firstly, because of the small number of patients, due to the rarity of the condition, conclusions should be interpreted with caution. Secondly, all data were collected retrospectively from patient records which increases the risk for information bias. Finally, since this is a single-centre study, some centre biases are present, for example in terms of choice and availability of SI.

In conclusion, the severity of hypokalaemia and hypercortisolaemia at diagnosis are associated with mortality in ECS. We also found that severe hypercortisolaemia was an independent bad prognostic factor regardless of the proliferation rate of the tumour. Even though accurate potassium substitution therapy is needed in the acute phase to prevent the risk of alkalosis, and SI therapy was used in the attempt to control hypercortisolaemia, most patients with severe hypokalaemia proceed to early BA or died within the first month. Therefore, we suggest that definite treatment of ECS should not be delayed, especially for patients with potassium levels <2.5 mmol/l. This implies discussions upfront regarding the possibility to carry out BA or radical tumour-directed surgery. Although multicentre studies in ECS with large, prospective cohorts are needed, the present study contributes to a better understanding of the clinical management of ECS.

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DISCLOSURE

The authors have declared no conflicts of interest.

REFERENCES

1. Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. *Lancet (London, England)*. 2015;386(9996):913-927.
2. Alexandraki KI, Grossman AB. The ectopic ACTH syndrome. *Rev Endocr Metab Disord*. 2010;11(2):117-126.
3. Schernthaner-Reiter MH, Siess C, Micko A, et al. Acute and life-threatening complications in Cushing syndrome: prevalence, predictors, and mortality. *J Clin Endocrinol Metab*. 2021;106(5):e2035-e2046.
4. Quinkler M, Stewart PM. Hypertension and the cortisol-cortisone shuttle. *J Clin Endocrinol Metab*. 2003;88(6):2384-2392.
5. Young J, Haissaguerre M, Viera-Pinto O, Chabre O, Baudin E, Tabarin A. Management of endocrine disease: Cushing's syndrome due to ectopic ACTH secretion: an expert operational opinion. *Eur J Endocrinol*. 2020;182(4):R29-R58.
6. Nieman LK, Biller BMK, Findling JW, et al. Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831.
7. Lase I, Strele I, Gronberg M, Kozlovacki G, Welin S, Janson ET. Multiple hormone secretion may indicate worse prognosis in patients with ectopic Cushing's syndrome. *Hormones (Athens, Greece)*. 2020;19(3):351-360.
8. WHO Classification of Tumours Editorial Board. *WHO Classification of Tumours*. *Digestive System Tumours: WHO Classification of Tumours, Volume 1*. World Health Organization; 2019.
9. Lase I, Grönberg M, Norlén O, Stålberg P, Welin S, Janson ET. Adrenalectomy in ectopic Cushing's syndrome: a retrospective cohort study from a tertiary care centre. *J Neuroendocrinol*. 2021;33(12):e13030.
10. Stachowska B, Kuliczkowska-Płaksej J, Kałużny M, Grzegrzółka J, Jończyk M, Bolanowski M. Etiology, baseline clinical profile and comorbidities of patients with Cushing's syndrome at a single endocrinological center. *Endocrine*. 2020;70(3):616-628.
11. Rosner MH, Dalkin AC. Electrolyte disorders associated with cancer. *Adv Chronic Kidney Dis*. 2014;21(1):7-17.
12. Lavoillotte J, Mohammedi K, Salenave S, et al. Personalized noninvasive diagnostic algorithms based on urinary free cortisol in ACTH-dependant Cushing's syndrome. *J Clin Endocrinol Metab*. 2024;109(11):2882-2891.
13. Torpy DJ, Mullen N, Ilias I, Nieman LK. Association of hypertension and hypokalemia with Cushing's syndrome caused by ectopic ACTH secretion: a series of 58 cases. *Ann N Y Acad Sci*. 2002;970(1):134-144.
14. Chen W, Chen L, Pei L, et al. Diagnostic strategy and prognostic factors for ectopic adrenocorticotropic hormone syndrome: a retrospective study of 64 cases. *Neuroendocrinology*. 2023;113(1):92-102.
15. Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. *Endocr Connect*. 2018;7(4):R135-R146.
16. Valassi E, Franz H, Brue T, et al. Preoperative medical treatment in Cushing's syndrome: frequency of use and its impact on postoperative assessment: data from ERCUSYN. *Eur J Endocrinol*. 2018;178:399-409.
17. European Medicines Agency. Ketoconazole HRA: summary of product characteristics. 2020. Available at https://www.ema.europa.eu/en/documents/product-information/ketoconazole-esteve-epar-product-information_en.pdf. Accessed May 5, 2025.
18. Varlamov EV, Han AJ, Fleseriu M. Updates in adrenal steroidogenesis inhibitors for Cushing's syndrome - A practical guide. *Best Pract Res Clin Endocrinol Metab*. 2021;35(1):101490.
19. Fleseriu M, Pivonello R, Young J, et al. Osilodrostat, a potent oral 11β-hydroxylase inhibitor: 22-week, prospective, phase II study in Cushing's disease. *Pituitary*. 2016;19(2):138-148.
20. Pivonello R, Fleseriu M, Newell-Price J, et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. *Lancet Diabetes Endocrinol*. 2020;8(9):748-761.
21. Tanaka T, Satoh F, Ujihara M, et al. A multicenter, phase 2 study to evaluate the efficacy and safety of osilodrostat, a new 11β-hydroxylase inhibitor, in Japanese patients with endogenous Cushing's syndrome other than Cushing's disease. *Endocr J*. 2020;67(8):841-852.
22. Bessiène L, Bonnet F, Tenenbaum F, et al. Rapid control of severe ectopic Cushing's syndrome by oral osilodrostat monotherapy. *Eur J Endocrinol*. 2021;184(5):L13.
23. Toivanen S, Leijon H, Arola A, et al. Characteristics and outcomes of the Finnish ectopic ACTH syndrome cohort. *Endocrine*. 2021;74(2):387-395.
24. de Bruin C, Feelders RA, Lamberts SW, Hofland LJ. Somatostatin and dopamine receptors as targets for medical treatment of Cushing's syndrome. *Rev Endocr Metab Disord*. 2009;10(2):91-102.
25. Phlipponneau M, Nocaudie M, Epelbaum J, et al. Somatostatin analogs for the localization and preoperative treatment of an adrenocorticotropin-secreting bronchial carcinoid tumor. *J Clin Endocrinol Metab*. 1994;78(1):20-24.
26. Bertagna X, Favrod-Coune C, Escourolle H, et al. Suppression of ectopic adrenocorticotropin secretion by the long-acting somatostatin analog octreotide. *J Clin Endocrinol Metab*. 1989;68(5):988-991.
27. Vignati F, Loli P. Additive effect of ketoconazole and octreotide in the treatment of severe adrenocorticotropin-dependent hypercortisolism. *J Clin Endocrinol Metab*. 1996;81(8):2885-2890.