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Paraneoplastic Cushing's Syndrome

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Abstract

Introduction: Paraneoplastic Cushing's syndrome is a condition representing a small-on average, a 10% fraction-of the cases of Cushing's syndrome and affects 1% - 5% of patients with small-cell lung cancer. Case Presentation: We presented a patient with paraneoplastic Cushing's syndrome due to small-cell lung cancer. Conclusion: This combination means a poorer prognosis with a shorter survival rate than other separate diagnoses.

Subject Areas

Diabetes & Endocrinology

Keywords

Paraneoplastic Cushing's Syndrome, Small-Cell Lung Cancer

1. Introduction

Paraneoplastic Cushing's syndrome (PCS) is a 5% - 15% fraction of the cases of Cushing's syndrome (CS) (67% had a pituitary origin and 15% - 25% an adrenal origin) [1]-[4]. PSC affects 1% - 5% of patients with small-cell lung cancer [4] [5]. The first step is laboratory tests with cortisol and ACTH levels to differentiate ACTH-dependent or ACTH-independent CS. When ACTH-dependent CS is confirmed, differentiation between PCS and Cushing disease is the next step. High-dose dexamethasone suppression tests help distinguish Cushing disease from PCS, as in our presented case. Clinical features of these patients include severe hypercortisolaemia, leading to low serum potassium levels, metabolic alkalosis, diabetes, generalized infections, hypertension, muscle weakness, and psychosis.

Treatment is mainly based on controlling the cortisol level and reducing tumor burden [6]. In paraneoplastic CS, malignancy is usually more extensive (discovered with 2 or more metastatic sites) with reduced response to first-line chemotherapy, excessive weight loss, a reduced performance score and greater susceptibility to infections. Administering chemotherapy in the immunosuppressive state induced by hypercortisolism, cancerous background, and metabolic disorders caused by electrolyte disturbance and hyperglycemia, aggravates the condition and can cause life-threatening complications like gastrointestinal ulceration, bleeding and severe infection. Thus, initiating the palliative approach can sometimes be reasonable. Sepsis can be the primary complication and cause of death [7].

2. Case Presentation

A 65-year-old patient with a history COPD, arterial hypertension, prosthesis right femoral artery, treated daily with: tiotropium/olodaterolum 2.5 ug, perindopril/amlodipin 10 mg/10mg, acetylsalicylicum 100 mg was addmited for the progression of dyspnea with positive rapid antigen COVID-19 test, and no verified PCR test. A few months preceded muscle weakness, swelling of the legs, and a progressive deterioration of the general condition. The objective finding was without signs of CS, and without hyperpigmentation. Computed tomography (CT) found a lung tumor in the right S2 segment, the size of which was 12 mm with adjacent atelectasis and fibrosis. Metastases in the liver were also present, and the S1 vertebra, left acetabulum, pubic bones, right sixth rib with pathological fracture and lung hilar, mediastinal, and right inguinal lymph nodes were also observed. This means extensive disease, ED, according to the histological classification of tumors, WHO 1981 [8]. Both adrenals were hyperplastic, without tumorous or metastatic masses. The right adrenal measured 12 × 29 × 60 mm, the left adrenal 17 × 32 × 75 mm. The results of CT scans are shown in **Figures 1-3**.

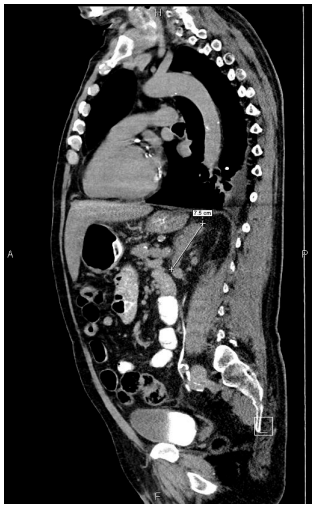

Figure 1. Left adrenal sagittal cut.

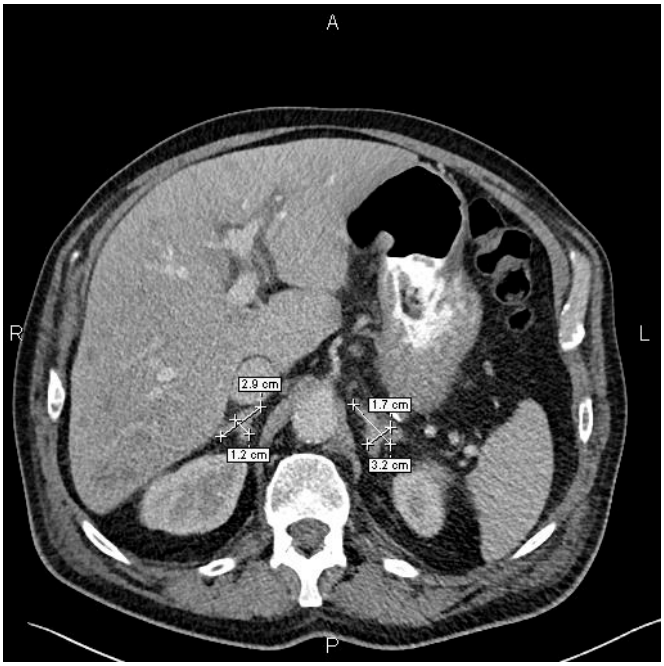

Figure 2. Adrenals transversal cut.

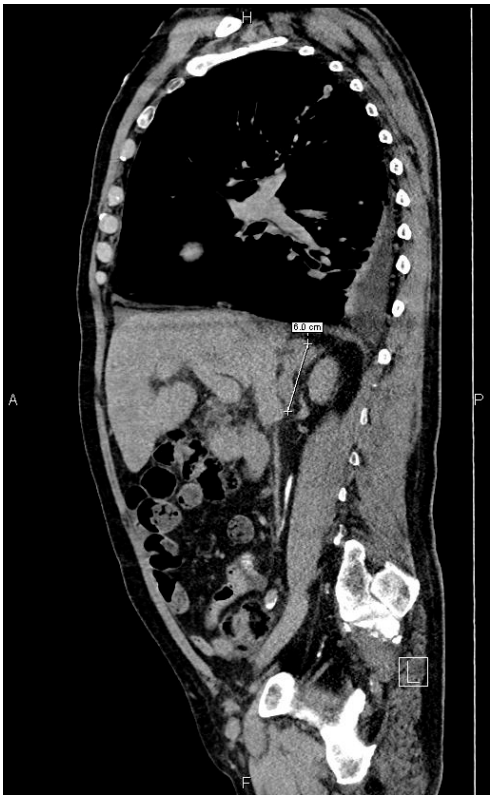

Figure 3. Right adrenal sagittal cut.

A biochemistry assessment showed metabolic alcalosis, hypokalemia, increased blood glucose, lymphopenia and lightly increased other biochemical parameters shown in **Table 1**.

Table 1. Biochemical parameters.

Parameter	Value	Normal ranges
pH	7.718	7.32 - 7.42
HCO_3	53.8 mmol/l	22 - 26
Potassium	1.7 mmol/l	3.5 - 5.3
Myoglobin	324.8 µg/l	<155
Glucose	8.5 mmol/l	3.9 - 5.6
AST	3.31 µkat/l	<0.59
ALT	2.4 µkat/l	<0.75
ALP	2.21 µkat/l	0.67 - 2.5
GMT	2.58 µkat/l	<1.07
CEA	114.95 µg/l	<5
CA 19-9	607 kU/l	<37
Chromogranin	1941 ng/ml	<85
Lymphocyts	1.1×10^9/l	0.8 - 4
	0.11%	0.2 - 0.45

Results of hormonal tests are shown in **Table 2**.

Table 2. Hormonal tests.

Parameter	Value	Normal ranges
Cortisol	6.00: 1680 24.00 1802 nmol/l	80 - 535
UFC	>3299 nmol/24 h	88 - 670
ACTH	448.9 ng/l	10 - 60
Cortisol overnight 1 mg dex	1963 nmol/l	<138
Cortisol overnight 8 mg dex	1960 nmol/l	

UFC: urinary free cortisol, dex: dexametasone.

These tests (high ACTH, high morning cortisol, high urinary free cortisol, high-dose dexamethasone non suppressible cortisol) are indicative of paraneoplastic CS.

According to the CT, the probable source of CS was a pulmonary tumor. The result of a bronchoscopy with bronchoalveolar lavage included result without malignant cells, therefore we performed a liver biopsy.

The CT-guided liver biopsy confirmed metastases from small-cell lung carcinoma. The anti-chromogranin, anti-synpatophysin antibodies stain was positive, and the Ki76 marker of proliferation activity was very high. Results of the liver biopsy are shown in **Figures 4-6**.

Our first aim was to decrease/normalise the secretion cortisol with Ketoconazole (600 mg/d) and after that to start chemotherapy. For metastatic spreading

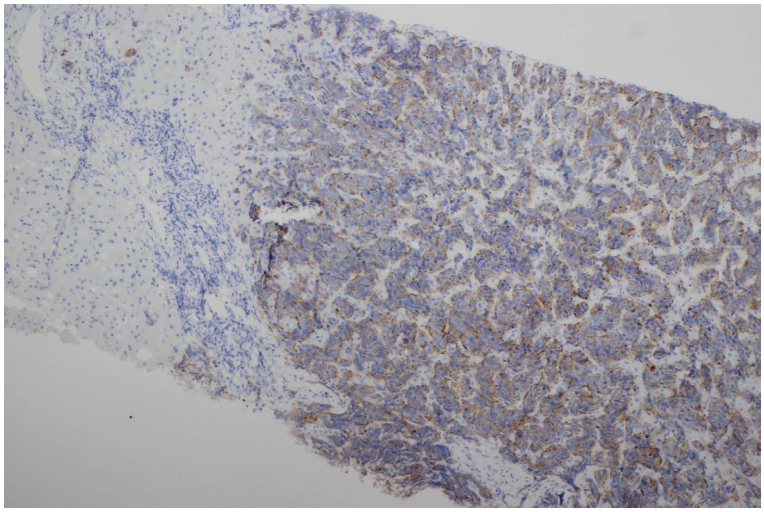

Figure 4. Liver biopsy synaptophysin staining.

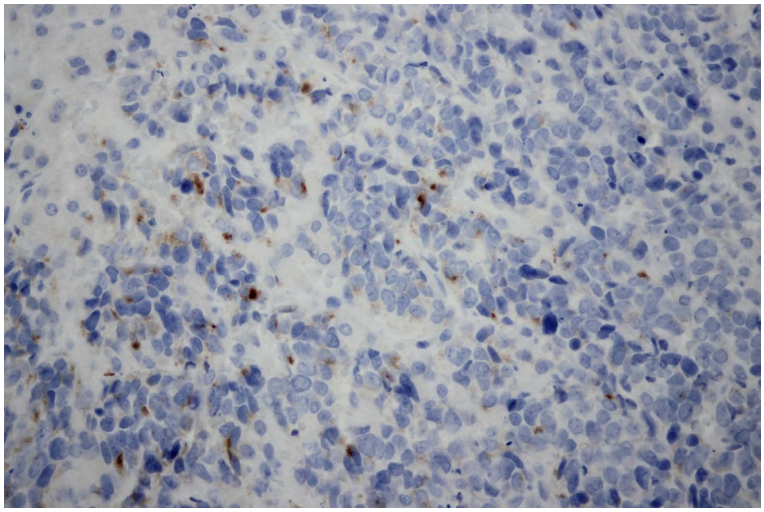

Figure 5. Liver biopsy chromogranin A staining.

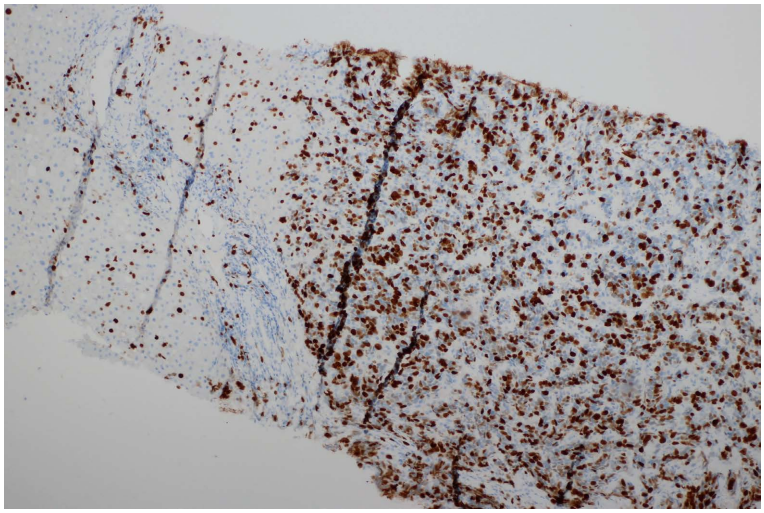

Figure 6. Liver biopsy Ki67 staining.

and infectious complications (pneumony with G-bacilli, incipient sepsis with staphylococcus aureus from a defect of the left big toe), radical palliative treatment (laparoscopic adrenalectomy) or chemotherapy was impossible. In short time ranging up to 1 month somatic status deteriorates with terminal cachexy, catabolism and serious infectious complications passed away and any more palliative therapeutical interventions were impossible in this period.

3. Discussion

The ideal treatment is curative surgery of the underlying tumor. If surgery is not curative due to metastatic spread, radio/chemotherapy and anticortisolic medication are recommended. First-line pharmacologic options for PCS are directed toward inhibiting steroid production. These drugs include ketoconazole, mitotane, metyrapone, and aminoglutethimide. Despite associated nausea and hepatotoxicity, ketoconazole is usually the best tolerated of these agents.

Bilateral adrenalectomy can resolve hypercortisolism in cases of non-operable or non-localized tumors or in cases where medical treatment is ineffective.

According to the literature review [9] to 2022, 61 reports with a total of 157 SCLC patients with PCS were published. This condition seems underdiagnosed and alongside PCS, is the worst form of paraneoplastic syndrome with particularly extensive tumours [7]. The median survival for patients with SCLS is 6.6 months with ACTH secretion compared with 13.1 months without ACTH secretion [10]. Therefore, these facts resulted in the importance of thinking about paraneoplastic CS in every malignancy with the presence of hypokalemia, metabolic acidosis, arterial hypertension and impaired glucose tolerance [6] [11], regardless of that a paraneoplastic syndrome may be the first sign of malignant disease.

Statement of Ethics

Ethical approval was not required for this study in accordance with local or national guidelines. Written informed consent for publication of this case report, and any accompanying images were obtained from the patient.

Author Contributions Statement

Alexander Kreze conceived the study, Alexander Kreze, Kristina Klemperová and Oliver Kuchař reviewed the literature, analyzed data and wrote the manuscript. Kristina Klemperová contributed to biochemistry, immunology, and hormonal analysis and interpretation. Martin Kucbel performed the radiodiagnostic imaging and interpretation, Hana Koutníková worked on biopsy exams and results. Kateřina Schwarzová was in-patient treating doctor. All contributors approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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