

APPARENT MINERALOCORTICOID EXCESS IN A CASE OF LUNG PARANEOPLASTIC CUSHING SYNDROME

C. Badiu¹, Cristina Capatana², D. Cristofor², G. Mircescu³, M. Coculescu^{*,1}

¹ "C. I. Parhon" Institute of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, Endocrinology Dpt., Bucharest

² "C. I. Parhon" Institute of Endocrinology, Bucharest

³ "Carol Davila" University of Medicine and Pharmacy, Nephrology Dpt.

Severe hypokalemia is a life threatening event, which triggers a number of therapeutic and diagnostic attitudes. In this paper we present a case of 63 years old man, who presented with progressive lassitude, edema, weight loss. The mild hypertension and hyperglycaemia were treated with spironolactone and diet. Initial evaluation showed severe hypokalemia (1.7 mmol/l), hepatomegalia, hyperplasic/nodular adrenal masses; in addition, he has developed a right middle lobe pneumonia which improved with antibiotics. Referred for the suspicion of hyperaldosteronism, aldosterone values were normal (9.3-9.5 µg/dl), but ACTH was high (725 pg/ml) and did not suppress (710.8 pg/ml) to high dose DXM, as well as cortisol: basal values 27.78 ug/dl, high dose DXM 35.06 ug/dl, showing an ACTH dependent Cushing syndrome despite lack of suggestive clinical signs. Tumor markers suggested a neuroendocrine neoplasia: carcinoembryonic antigen=101 ng/ml (normal values=0.52-6.3 ng/ml), CA 19-9= 155 ng/ml (N < 33 ng/ml). Further radiological evaluation showed a 3 cm right lobe lung tumour. Despite high potassium supplements and spironolactone, the hypokalemia remained around 3.2 mmol/l, characteristic for an apparent mineralocorticoid excess. Because of aggressive evolution of the lung tumour, he died three months after the initial admission into the hospital. Pathology report showed a lung carcinoma. ACTH immunostaining of the lung tumour was positive and revealed a paraneoplastic secretion.

Key words: ACTH, lung cancer, hypokalemia, paraneoplastic Cushing syndrome, mineralocorticoid.

*Correspondence to: Mihai Coculescu, Endocrinology Department, "Carol Davila" University of Medicine and Pharmacy, 34-36 Bd. Aviatorilor, 011863, Bucharest, Romania, Tel/Fax: + 4021 3198718, e-mail: m.coculescu@uni-davila.ro

INTRODUCTION

Spontaneous hypokalemia is a life threatening condition which might appear due to a variety of disorders. Although its cause is usually apparent from the history and the clinical setting there are cases where the differential diagnosis of hypokalemia represents a great challenge for the physician. The most useful clinical classification of hypokalemic disorders is to divide them in normotensive and hypertensive groups. Diuretics-related hypokalemia must be excluded. Acid-base parameters and urinary ionogram are the next important step to make a diagnosis. Hypertension together with hypokalemia and metabolic alkalosis is a common clinical problem, often a consequence of mineralocorticoid excess, either primary or secondary. Other rare mineralocorticoid excess states (ingestion of compounds such as glycyrrhizic acid and carbenoxolone or of the rare genetic disease known as apparent mineralocorticoid excess) can also be responsible for this triad. Cushing's syndrome can also lead to hypokalemia and hypertension, more commonly in cases of ectopic Cushing's syndrome (excess ACTH secretion by an extrapituitary tumor) (1).

Ectopic ACTH hypersecretion is a rare cause of ACTH-dependent Cushing's syndrome (approximately 5-10% of cases of spontaneous Cushing's syndrome). The four most common causes of ectopic ACTH syndrome are the small cell lung carcinoma (SCLC) (27%), bronchial carcinoids (21%), islet cell tumor of the pancreas (16%), and thymic carcinoids (10%) (2).

Patients with ectopic ACTH syndrome often lack the classic clinical features of Cushing syndrome especially in cases secondary to small cell lung cancer (disease so rapidly progressive that few patients with ectopic ACTH production live long enough to develop the clinical signs of Cushing syndrome). Among the features most frequently met are hydroelectrolytic and metabolic abnormalities, weight loss, proximal myopathy and hyperpigmentation caused by excessive levels of ACTH. Also, because of the dominant prevalence of lung cancer in these cases, males are affected more commonly, usually at older ages than in classic Cushing's syndrome.

In this report we present a case of paraneoplastic hypokalemia in a patient with undifferentiated lung cancer.

CASE REPORT

The patient, a 63 year-old male, was a heavy smoker with no significant past medical history. He had been well until 2 months prior to his admission in our clinic. At that time he started to accuse intense fatigue, loss of appetite and progressive peripheral edema. He was admitted to an internal medicine department where moderate peripheral edema and important hepatomegaly were noted on the clinical examination. The laboratory tests revealed severe hypokalemia (K = 1.7 mmol/l) and metabolic alkalosis and progressive normochromic,

normocytic anemia. A mild diabetes mellitus was also diagnosed. At the same time he developed a right middle lobe pneumonia (presenting as productive cough, coarse rales over the right hemithorax and an ovalar opacity in the middle right lobe of the lung). This was considered a hospital respiratory tract infection, cured under antibiotic treatment with disappearance of abnormal image at radioscopic control. Under intensive intravenous K supplementation and high doses of spironolactone serum level of potassium rose very slowly (up to a maximum of 2 mmol/l) and the patient's condition worsened: he began to feel very weak and could not walk without support. Over one month he lost about 10 kilos. As part of the general investigation an abdominal computed tomography was made that showed enlarged adrenal glands with macronodular appearance. Taking into account the severe hydroelectrolytic abnormality a suspicion of primary hyperaldosteronism was raised and the patient was referred to our clinic for further investigation.

On admission in our department he was afebrile and displayed intense lassitude with marked reduction of muscle strength of the lower limbs. No other neurologic abnormality was found. Important edema of the lower legs and dorsum of the hands, dry, pale skin and discrete hyperpigmentation of the upper thorax were noted. His BP was 155/90 mmHg, pulse rate 74 beats/min with many extrasystoles (around 10-12 per minute), without any murmurs. He was not dyspneic and had no jugular venous distention but he had productive cough and coarse rales were localized in the inferior third of the posterior thorax. Non-tender hepatomegaly was present, extending approximately 5 cm below the rib cage, of firm consistency, without concomitant spleen enlargement or ascites. The day prior to admission the patient had gross hematuria without any associated symptom.

Routine laboratory data revealed normochromic, normocytic anemia (Hb = 9.7 g/dl, Ht = 26.5%), a slightly elevated leucocyte count, moderate hyperglycemia (between 1.9 and 2.5 mmol/dl), marked hypoproteinemia (4.94 g/dl) that rose up to 5.16 g/dl with albumin administration, severe metabolic alkalosis (pH = 7.61, HCO₃ = 53.8 mmol/l, pCO₂ = 54.7 mmHg) and severe hypokalemia (1.9 mmol/l at admission, rose up to 2.4 mmol/l under treatment with spironolactone and K supplementation). Liver and kidney function tests were normal. Urine examination showed glycosuria (100 mg/l), microhematuria, increased urinary potassium loss (between 24.3 and 50.9 mmol/l - highest values being measured under intensive K supplementation) and proteinuria (between 165 and 540 mg/l).

For investigation of hepatomegaly we performed Ag HBs, anti HVC Ab tests - both were negative. As tumoral markers we measured: carcinoembryonic antigen = 101 ng/ml (normal values 0.52-6.3 ng/ml), CA 19-9 = 155 ng/ml (N <33 ng/ml), alpha fetoprotein = 1.71 pg/ml and prostate specific antigen = 0.71 ng/ml; the first two markers had elevated values, suggesting a neoplasia.

The value of plasma aldosterone was normal (9.32 ug/dl) both under basal conditions and after two days of dexamethasone administration (2 mg/day) - 9.50 ug/dl. A plasma renin activity measurement was not available. The

electrocardiogram shows coupled ventricular extrasystoles and a long QT interval, in accordance with hypokalemia (Fig. 1).



Figure 1. Electrocardiogram (single black arrows are used to mark coupled ventricular extrasystoles, double arrow mark the long QT interval - msec).

Echocardiographic examination revealed hypertrophy of the interventricular septum but normal values for other standard parameters (including ejection fraction).

Pulmonary X-ray examination revealed next to the right pleura an irregular mass, 3 cm wide (Fig. 2).

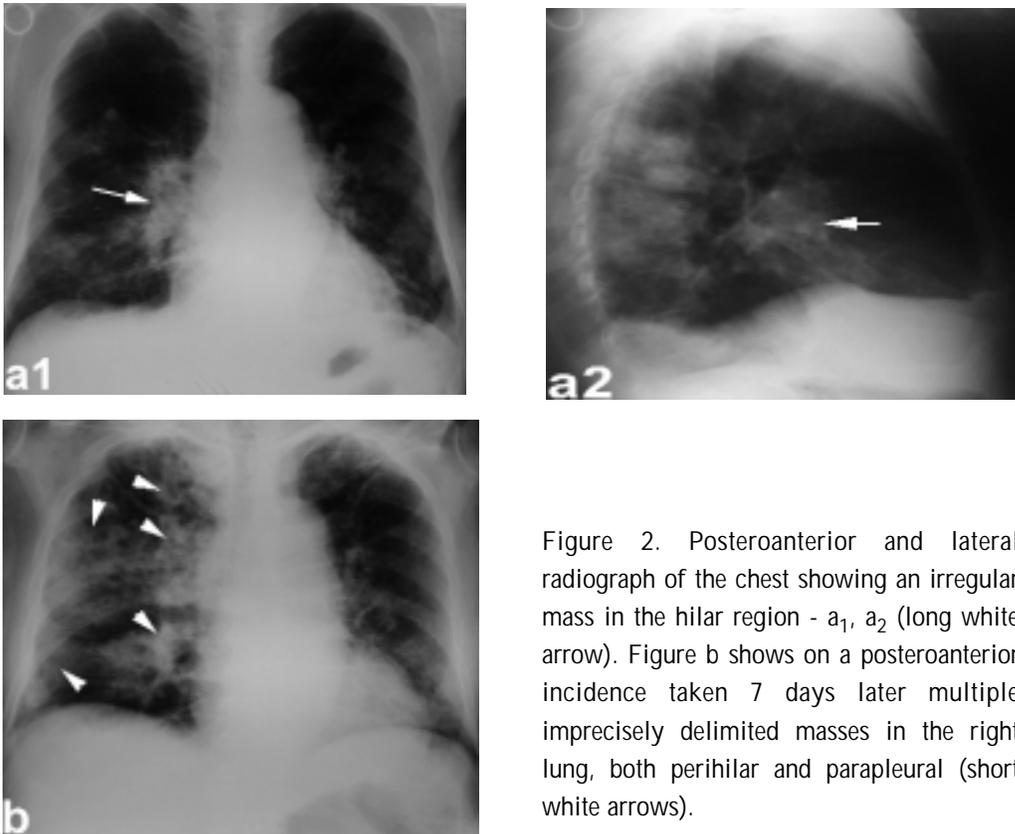
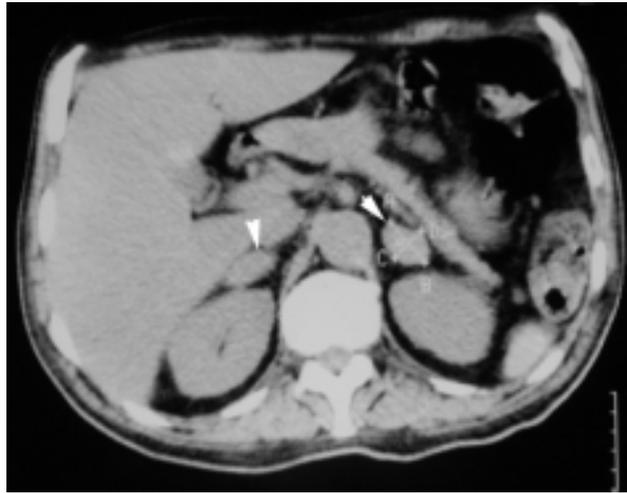


Figure 2. Posteroanterior and lateral radiograph of the chest showing an irregular mass in the hilar region - a₁, a₂ (long white arrow). Figure b shows on a posteroanterior incidence taken 7 days later multiple imprecisely delimited masses in the right lung, both perihilar and parapleural (short white arrows).

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Abdominal computed tomography revealed hepatomegaly and bilateral adrenal macronodules (15/31 mm on the right side and 19/28 mm on the left) (Fig. 3).

Figure 3. Abdominal contrast enhanced CT scan showing bilateral enlarged adrenal glands (white arrows).

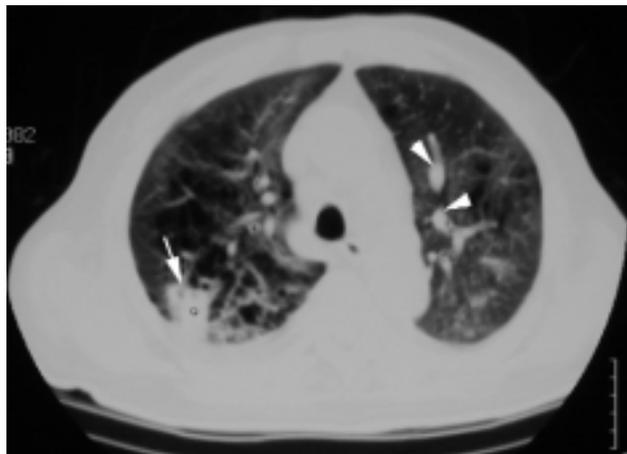


The patient received potassium supplement with potassium chloride 7.45% solution 60 mEq intravenous daily and 4-6 g potassium chloride *per os* daily. In addition he received spironolactone 300 mg/day, albumin, antiarrhythmic treatment with propafenone, sulphonylurea and perindopril for the control of BP. With this treatment the edema diminished, the extrasystoles persisted reflecting the partial resistance of serum potassium level to supplementation.

We interpreted the association of hematuria, proteinuria, edema and mild hypertension as well as the relative lack of response of urinary potassium loss to treatment as signs of a glomerular disease and after performing all the necessary endocrine tests we referred the patient to a nephrology department.

There a thoracic computed tomography was performed that revealed a right pulmonary tumor (Fig. 4).

Figure 4. Contrast-enhanced thoracic computed tomography showing in the dorsal segment of the inferior lobe of the right lung a solid mass with irregular borders, in contact with visceral pleura (long white arrow). At various levels in both lungs other solid inhomogeneous images with irregular contours are visible (short white arrows).



Fiberoptic bronchoscopy, sputum cytology and percutaneous aspiration biopsy could not be performed in the precarious clinical condition of the patient. Also, a renal biopsy was not taken.

While the patient was being investigated in the nephrology department the results of the endocrine tests became available: serum basal cortisol was 27.78 ug/dl and serum cortisol after high dose dexamethasone (8mg q.d. for 2 days) was not suppressed (35.06 ug/dl). ACTH levels were highly elevated (725.4 pg/ml basal and 710.8 pg/ml after dexamethasone administration) so the diagnosis of ACTH-dependent Cushing syndrome became obvious.

In the meantime the condition of the patient worsened significantly (despite a constant increase in potassium levels up to 3.8 mmol/l) and within 2 days he died from respiratory insufficiency. Postmortem pathological examination revealed ulcerated mass in the right inferior pulmonary lobe that proved to be undifferentiated lung carcinoma with bilateral pleural and ganglionic metastases. Immunohistochemical analysis showed that tumoral tissue was positive for ACTH (Fig. 5).

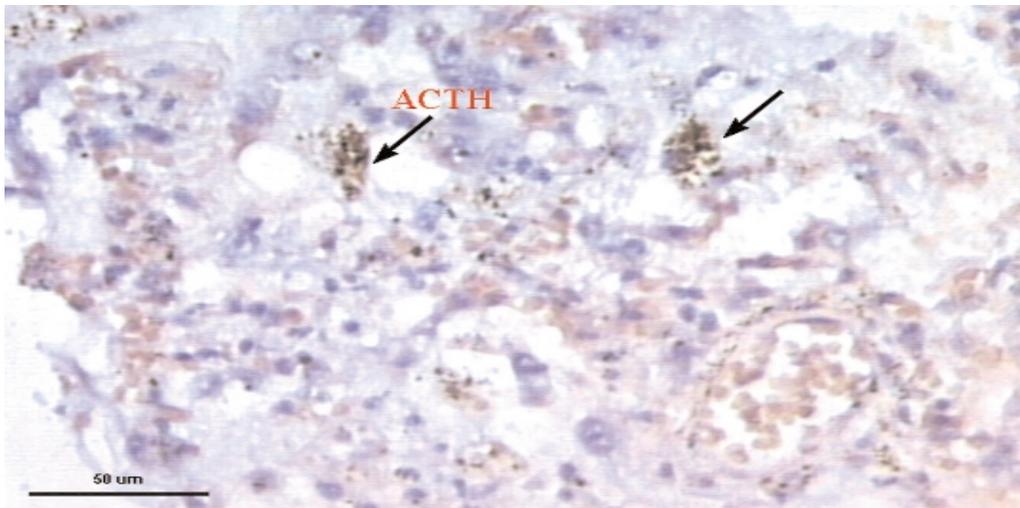


Figure 5. ACTH immunostaining in the lung tumor showing nests of cells ABC method, polyclonal rabbit antihuman ACTH antibody, HE counterstaining, $\times 400$.

DISCUSSION

The main problem of the case at presentation was severe hypokalemia. The differential diagnosis of hypokalemia is depicted in Fig. 6. Once we have excluded spurious hypokalemia, situations associated with potassium redistribution and decreased intake, the next step is to determine whether potassium is lost through kidney or at extrarenal sites (mostly gastrointestinal) by appreciation of urinary potassium. If urinary excretion of potassium is greater than 20 mmol/l it strongly

suggests renal potassium loss. Assessments of acid-base balance and urinary ionogram are necessary.

Renal potassium loss, associated with metabolic alkalosis and low urinary chloride, recognizes as the most probable cause diuretic use. In cases with high urinary chloride, mineralocorticoid excess is possible. In a hypertensive patient, as was our own, the next useful step is measurement of aldosterone. A high level suggests primary or secondary hyperaldosteronism; if the level is normal, the cause most frequently met is Cushing syndrome (3). Approximately one-third of cases of Cushing's syndrome have K⁺ depletion, and hypokalemia is the most frequent in patients with ectopic ACTH production (4). Hypokalemia, which is seen in up to 90% of cases (5) in the setting of ectopic ACTH secretion, is caused by a mineralocorticoid-excess state. This is mainly due to the very high levels of cortisol. This overwhelms the capacity of renal 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD₂). This enzyme metabolizes cortisol to cortisone, which has much less biological activity and so protects the renal mineralocorticoid receptor from cortisol binding. An alternative explanation is that high levels of ACTH inhibit the action of 11 β HSD₂, either directly or by stimulating the synthesis of an inhibitory product (6). To dyselectrolythemia also contributes the excess synthesis of corticosterone and deoxycorticosterone (7).

Saturation of renal 11 β hydroxysteroid dehydrogenase by extremely high levels of cortisol is the main physiopathologic mechanism. Such being the case it is not surprising that several studies showed that hypokalemia correlates with cortisol levels (8) so severe hypokalemia is indirectly associated with an ominous prognosis. In the rare cases where cortisol and aldosterone levels are normal the diagnosis is oriented toward other entities with high concentrations of mineralocorticoids other than aldosterone (with these conditions aldosterone and plasma renin activity are suppressed) or Liddle syndrome. Also, there are cases with high urinary chloride in a normotensive patient; these suggest a group of very rare conditions like Bartter's or Gitelman's syndromes (3).

In our case the suspicion of mineralocorticoid excess was legitimate. Moreover, the mild hypertension associated with hypokalemic alkalosis strengthened the first clinical impression. Yet the association of peripheral edema is an extremely rare occurrence in primary hyperaldosteronism. Also the patient did not present classic features of any of the diseases associated with secondary hyperaldosteronism. The normal value of plasma aldosterone did not support this diagnosis.

Moderately high values of cortisol without suppression during the high dose dexamethasone suppression test and extremely high levels of ACTH set the diagnosis of ACTH dependent Cushing syndrome - probably caused by an ectopic tumor (given lack of suppression of cortisol levels and extremely elevated ACTH). The association of ACTH dependent hypercortisolism with marked hypokalemia, proximal myopathy, peripheral edema, hyperpigmentation in the absence of characteristic cushingoid appearance was also strongly suggestive of paraneoplastic

Cushing's syndrome. The association of high levels of carcinoembryonic antigen (CEA) strengthened the suspicion. Ectopic tumors may express and cosecrete many peptides (calcitonin, somatostatin, gastrin, pancreatic polypeptide, vasoactive intestinal peptide, glucagon, hCG- β , α -fetoprotein, α -subunit, neuron-specific enolase, GHRH, CRH and CEA (9) so the association of any of these with excessive ACTH secretion makes a diagnosis of ectopic secretion more likely. Since lung tumors are among the most frequent causes of ectopic Cushing's syndrome, the discovery of the lung tumor with aggressive clinical behaviour was not unexpected. The final proof of the diagnosis in our case is demonstration of the hormone in tumor tissue (alternatively it could have been demonstration of an expression of hormone messenger RNA by tumor or improvement of hormonal syndrome with successful therapy for the lung tumor).

Based on retrospective surveys, ectopic ACTH secretion had been diagnosed in less than 5 per cent of patients of small-cell lung cancer (10) yet ectopic ACTH secretion occurs in 50% of patients with SCLC (11). The rest of the patients probably secrete ACTH precursors that may have reduced bioactivity and so do not give rise to symptoms of hormonal overproduction (12)

Both normal lung tissue and lung carcinomas contain POMC and related peptides. In normal lung there is a predominance of smaller incomplete forms of POMC mRNA, but lung neoplasms contain the complete form of POMC mRNA so they can synthesise both POMC and all related peptides (13). Secretion of POMC - derived peptides by non-pituitary tumors is essentially different from the process that normally takes place in the pituitary in that it produces high amounts of large cleavage fragments not normally seen in the pituitary (14). The explanation is that transcription of the POMC gene is under the control of three promoter regions. In normal pituitary the P₂ promoter is active, while in cancer-associated ACTH production, the P₁ promoter predominates (15). Actually in patients with ectopic ACTH syndrome levels of ACTH precursors are often very high and in some cases may represent the predominant circulating form (16). Thus, detecting abnormal peptides (CLIP, β MSH, γ MSH) in plasma might help to orientate the diagnosis to an ectopic ACTH hypersecretion (17)

In our case the discrepancy between extremely high levels of ACTH and moderately elevated cortisol levels can be explained by the predominance of biologically inactive ACTH and precursors over the active form of the molecule. Detection of ACTH precursors is usually accomplished by two-site immunoradiometric assay (IRMA). When using radioimmunoassay (as we did) some or most of the ACTH immunoreactivity measured could be due to cross-reactivity of ACTH precursors in the ACTH RIA.

As for the adrenal bilateral masses, a macronodular bilateral hyperplasia can be a consequence of ACTH excess, but at the same time it could represent bilateral adrenal metastases since adrenal glands are a common site of metastasis for lung cancer and the usual hematogenous way of spread makes it possible for both adrenals to be involved (18).

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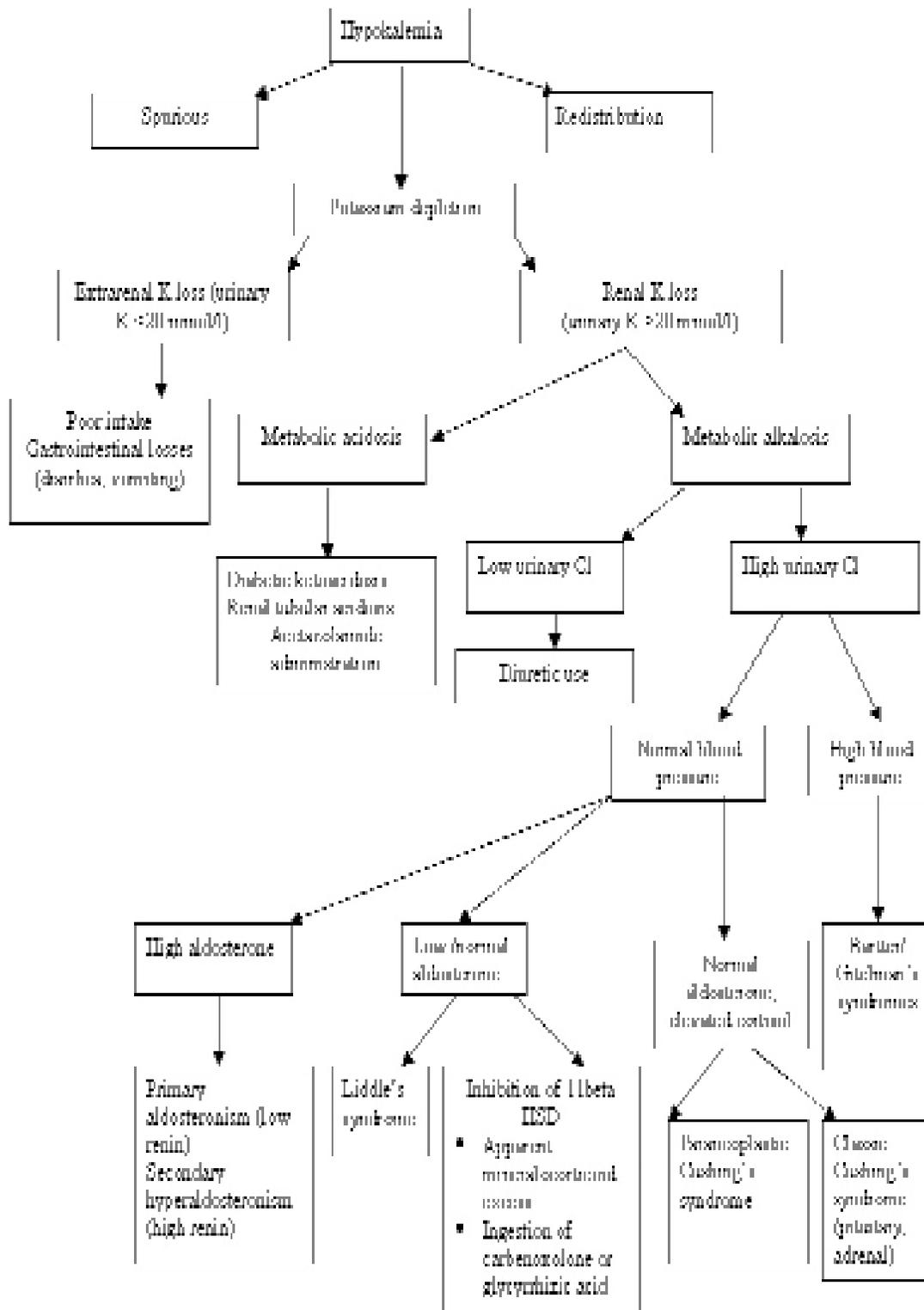


Figure 6. Algorithm for differential diagnosis of hypokalemia.

As for hypokalemia the classic mechanism involves decreased activity of 11β HSD₂ via several mechanisms explained above. The appearance of glomerular injury (membranous glomerulonephritis) as a paraneoplastic lung event is quite rare but it is associated with a poor prognosis (19, 20).

Given the fulminant evolution a treatment with inhibitors of glucocorticoid biosynthesis was not instituted, nor was it enough time for initiation of chemotherapy. Treatment options would have included inhibitors of steroid biosynthesis such as metyrapone, ketoconazole, and aminoglutethimide, but response is poor to either of them. Another theoretical method to suppress ACTH production would be octreotide (because almost 90% of tumors involved in ectopic ACTH production are neuroendocrine tumors with somatostatin receptors). In addition, octreotide can be used as a radiotherapeutic pharmacological agent or to enhance the efficacy of chemotherapy (24), but data related to its efficacy in ectopic ACTH syndrome are few to date. Mitotane cannot be used because its action is too slow for this clinical situation. As for chemotherapy, the small cell lung cancer (SCLC) associated with the EAS is more resistant to chemotherapy and the severe hypercortisolism is responsible for a high rate of life-threatening complications during treatment (21). Although chemotherapy prolongs median survival rates in SCLC up to 12-15 months, the presence of paraneoplastic hypercortisolism is associated with a survival of only 1 - 3 months despite chemotherapy. Partially responsible for that poor response are the opportunistic infections fostered by cortisol excess (22, 23).

In conclusion, this clinical case presentation illustrates many of the characteristic features of a lung tumor with paraneoplastic ACTH syndrome and the fact that ectopic Cushing syndrome can be suspected on the basis of severe hypokalemic alkalosis of recent onset.

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