Endocrinology, Diabetes & Metabolism CASE REPORTS

A Taieb and others | Endocrinological metastasis in lung cancer

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Multiple endocrinological failures as a clinical presentation of a metastatic lung adenocarcinoma

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Summary

Multiple endocrine metastases are a rare but possible complication of lung adenocarcinoma (LAC). Pituitary metastasis is a rare condition with poor clinical expression. Diabetes insipidus (DI) is its most common presenting symptom. Here we report an original case of a pituitary stalk (PS) metastasis from LAC presenting as central DI followed by adrenal insufficiency (AI) from bilateral adrenal metastasis, without known evidence of the primary malignancy. A 45-year-old woman whose first clinical manifestations were polyuria and polydipsia was admitted. She was completely asymptomatic with no cough, no weight loss or anorexia. Chest radiography was normal. Brain MRI showed a thick pituitary stalk (PS). DI was confirmed by water restriction test and treated with vasopressin with great clinical results. Explorations for systemic and infectious disease were negative. Few months later, an acute AI led to discovering bilateral adrenal mass on abdominal CT. A suspicious 2.3 cm apical lung nodule was found later. Histopathological adrenal biopsy revealed an LAC. The patient received systemic chemotherapy with hormonal replacement for endocrinological failures by both vasopressin and hydrocortisone. We present this rare case of metastatic PS thickness arising from LAC associated with bilateral adrenal metastasis. Screening of patients with DI and stalk thickness for lung and breast cancer must be considered. Multiple endocrine failures as a diagnostic motive of LAC is a rare but possible circumstance.

Learning points:

- Adrenal metastasis is a common location in lung adenocarcinoma; however, metastatic involvement of the pituitary stalk remains a rare occurrence, especially as a leading presentation to diagnose lung cancer.
- The posterior pituitary and the infundibulum are the preferential sites for metastases, as they receive direct arterial blood supply from hypophyseal arteries.
- Patients diagnosed with diabetes insipidus due to pituitary stalk thickness should be considered as a metastasis, after exclusion of the classical systemic and infectious diseases.
- The diagnosis of an endocrinological metastatic primary lung adenocarcinoma for patients without respiratory symptoms is often delayed due to a lack of correlation between endocrinological symptoms and lung cancer.
- The main originality of our case is the concomitant diagnosis of both endocrinological failures, as it was initiated with a diabetes insipidus and followed by an acute adrenal insufficiency.

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Background

Lung cancer (LC) remains one of the most frequently diagnosed cancers worldwide and a leading cause of cancer death among both males and females (1). Around the world, LC rates are decreasing in both males and females, thanks to sensibilization campaigns. Of the several types of LC, the presence of lung adenocarcinoma (LAC) is strongly linked to risk factors such as tobacco abuse (2).

While LAC rarely metastasizes to unusual locations, they most commonly do to the liver, adrenal glands and bones (3). Between 28 to 42% of LAC and approximately 30% of breast cancers metastasize to the adrenals (4). Adrenal insufficiency (AI), occurs in approximately 3 to 8% of individuals with bilateral adrenal metastases (5). AI was most commonly seen in bilateral adrenal metastases from LC (4).

Even if adrenal metastasis seems a common location in LAC, metastatic involvement of the pituitary stalk (PS) remains a rare occurrence, especially as a leading presentation to diagnose an LAC. Histological subtypes of primary tumors which have been documented to spread to the pituitary include LC, breast cancer and prostate cancer, with LAC being the most frequently reported (6). Clinical presentations range from isolated diabetes insipidus (DI) to panhypopituitarism, especially if the pituitary gland is affected (7).

It is assumed that revealing an LAC at a metastatic stage might worsen the prognosis and decrease life expectancy with increasing number of metastatic organs (1). The involvement of two or more metastatic sites was a significant predictor for a worse prognosis. Even if discovering LAC at multiple metastatic organs stage is not uncommon, very rare cases studied the association of multiple endocrinological failures in this cancer (8).

Despite this knowledge, the diagnosis of primary LAC for patients without respiratory symptoms is often delayed due to a lack of correlation made between endocrinological symptoms and LC.

Herein, we report a very rare case of PS metastasis from LAC first presenting as central DI followed by an acute AI leading to discovery of bilateral adrenal metastasis, without known evidence of the primary lung malignancy.

Case presentation

A 45-year-old woman with a 30-pack a year smoking history presented with a medical history of controlled hypertension with anti-hypertensive medications and dietetics measures. She had a 2-month history of polyuria, polydipsia and asthenia. She did not have anorexia or weight loss. She had normal menstrual cycles. The patient had no fever, cough, dyspnea, hemoptysis or chest pain. Physical examination was totally normal.

She presented to the department of Endocrinology in Douai Hospital Center, and the investigation at that time showed a fasting plasma glucose level of 5 mmol/L excluding diabetes. Laboratory tests showed a serum sodium level of 138 mmol/L; a potassium level of 3.9 mmol/L, clearance of 110 mL/min and a urine specific gravity of 1.002 without proteinuria or glycosuria. The 24-h urinary volume was of 6 L. Hormonal analyses showed a baseline serum cortisol concentration of 12.8 µg/dL (normal range (NR): 5–25 µg/dL) with a normal ACTH of 33.8 pg/mL (NR: 10–55 pg/dL). Thyroid function tests revealed a normal serum triiodothyronine (T3), thyroxine (T4) levels and a normal thyroid stimulating hormone level of 3.6 mIU/L (NR: 0.27–4.0 mIU/L). The rest of the anterior pituitary axes were normal, including the prolactin level.

Investigations

AWater deprivation and vasopressin challenge tests were done to confirm the central DI. The test was stopped at the fifth hour, after the patient had presented an intolerance to thirst. The initial serum osmolarity was 289 mosmol/kg, whereas the urine osmolarity and urine specific gravity were of 86 mosmol/kg and under 1.005, respectively. The 5-h water deprivation test started at 08 AM The urine osmolarity did not increase above 200 mosmol/kg (maximal increase at 129 mosmol/kg), eventhough almost 1.6 kg of weight loss had occurred.

However, it increased to 215 mosmol/kg (a 60% increase) 60 min after an s.c. injection of 5 U of vasopressin (Table 1).

Central DI was diagnosed based on a decrease in the urine output and an increase in more than 60% in urine osmolality in response to vasopressin.

Given the diagnosis of central DI, further investigations including MRI of the pituitary gland were made. MRI of the pituitary gland revealed a thick PS (4 mm), as shown in Fig. 1, a markedly decreased signal intensity of the posterior pituitary gland in the T1-weighted MRI, with normal-appearing pituitary gland (Fig. 2). The patient was then treated with vasopressin.

Based on these discoveries, inflammatory, autoimmune and infiltrative granulomatous disorders were evoked and searched by clinical and biological explorations. Serum calcium was 2.40 mmol/L. Erythrocyte sedimentation

Table 1 Clinical and biological characteristics during water deprivation and vasopressin challenge tests.

Tests	H0	H1	H2	H3	H4	H5*	H6	H7
Natremia (mmol/L)	140	139	141	140	142	143	144	144
Plasma osmolarity (mosmol/kg)	289	290	291	292	296	297	301	304
Plasma creatinine (mg/L)	6	6	6.3	5.9	6.4	6.6	6.9	7
Plasma urea (g/L)	0.19	0.19	0.19	0.19	0.18	0.18	0.19	0.19
Hourly diuresis (mL/h)	350	300	200	300	200	200	80	30
Urinary density	1.005	1.005	1.005	1.005	1.005	1.005	1.015	1.02
Urinary osmolarity (mosmol/kg)	86	90	96	105	129	115	215	432
Weight (kg)	87.2	86.9	86.7	86.3	86.1	85.9	85.7	85.6
Weight loss (kg)	0	0.3	0.5	0.9	1.1	1.3	1.5	1.6
Arterial pressure (mmHg)	110/76	120/72	133/83	122/52	136/104	135/83	141/95	147/88

*5 UI of Vasopressin.

rate, ACE-levels, ferritin and autoantibodies including cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA) were normal/negative. A chest X-ray showed no identifiable lung mass or abnormalities (Fig. 3).

Outcome and follow-up

Three months later, the patient presented with asthenia, hypotension, nausea and abdominal pain. She never stopped her treatment with vasopressin. High serum potassium (6.0 mmol/L) and mild hyponatremia (127 mmol/L) were discovered. Hormonal analyses showed a baseline serum cortisol concentration of 1.44 µg/dL, and the peak cortisol response to 250 µg of adrenocorticotropic hormone (ACTH) stimulation test was of 1.50 µg/dL. ACTH serum level was very high (133 pg/mL), confirming the primary AI.

Abdomen contrast CT and adrenal MRI exams were performed and a bilateral adrenal hypertrophy with hypertrophy was found (Fig. 4). The adrenal aspects had an increased attenuation (>30 Hounsfield units) and heterogeneous appearance.

Thorax CT showed a 23 mm apical opacity in the right lung with a unique right latero-tracheal adenopathy (Fig. 5).

A PET-scan showed a hyper fixation in the right apex's mass and in both adrenal glands. The pathological examination of the adrenal biopsy specimen after ruling out pheochromocytoma and Conn disease was consistent with LAC, without expression of ALK ROS1, EGFR. The PDL-1 was under 50%. A *TP53* mutation was discovered later on.

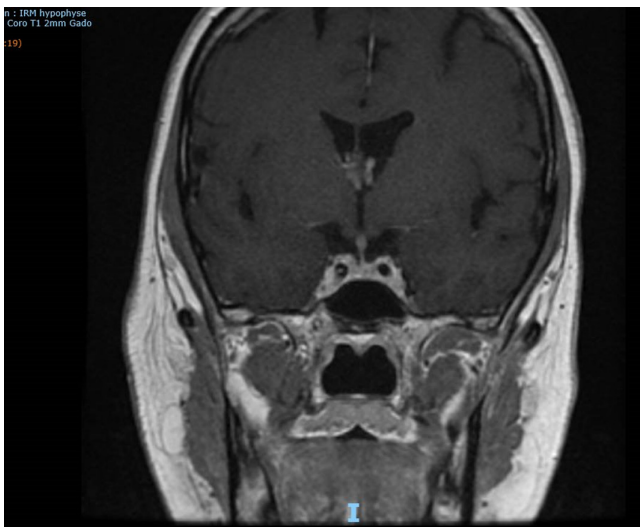

Figure 1
Pituitary MRI with gadolinium contrast, Coronal T1W image showing a thickened pituitary stalk of 4 mm and a markedly decreased signal intensity of the posterior pituitary gland.

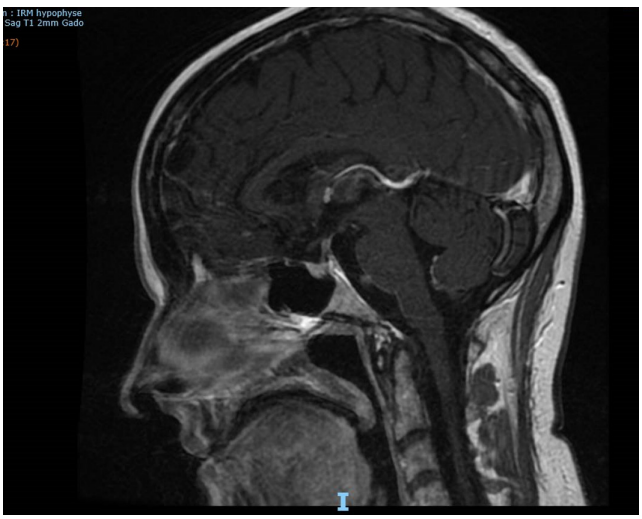

Figure 2
Pituitary Sagittal T1W MRI image showing a decreased signal intensity of the posterior pituitary gland.

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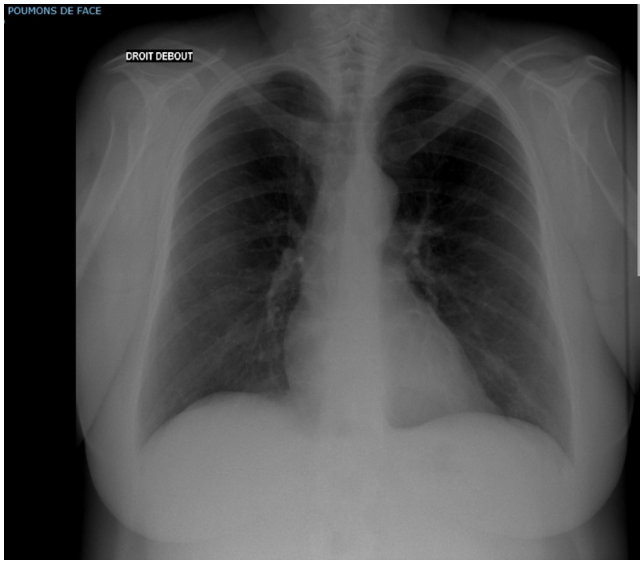

Figure 3
Chest radiography with no remarkable lung mass.

As a result, the diagnosis of stage IV LAC was established and thus the patient has undergone chemotherapy with Cisplatine (145 mg) and Pemetrexed (950 mg). After 3 months of regular follow-up, pituitary control MRI showed a normal pituitary stalk. Hormonal control assessment showed a persistent adrenal insufficiency. Attempting to stop the vasopressin treatment led to the reoccurrence of polyuria and polydipsia, confirming the persistence of DI.

Discussion

The current case report is among the rarest to report a patient with primary LAC with concomitant PS and

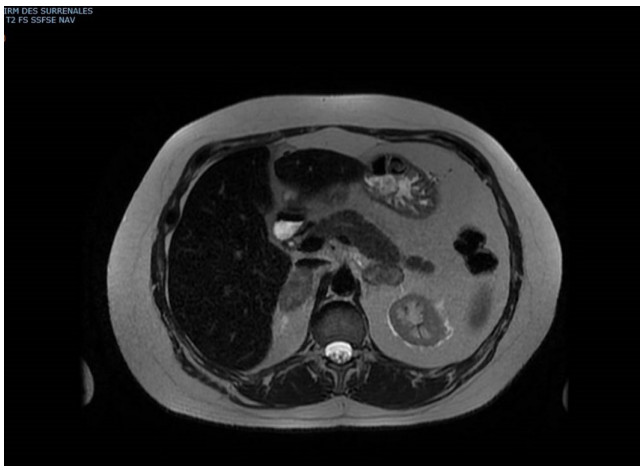

Figure 4
Adrenal MRI with T2W Fat Sat image showing a bilateral adrenal mass with micronodular hyperplasia.

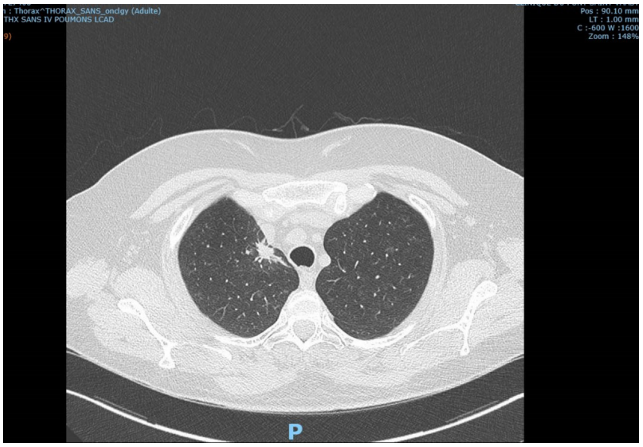

Figure 5
CT scan of the chest demonstrating a 2.3 cm right superior hilar mass suspicious for pulmonary malignancy.

bilateral adrenal metastasis. Pulmonary adenocarcinoma, a subtype of the non-small cell type, is the most common type of LC (3). A group study analyzed subtypes of LC and found that small cell LC most commonly metastasizes to liver and CNS, while LAC metastasizes frequently to bone and respiratory system (9). Very few cases studied pituitary involvement as a metastatic location, especially targeting the stalk. Metastatic lesions account for about 1% of all sellar and parasellar pituitary tumors (10).

LC is the second most frequent type of malignancy to metastasize to the pituitary gland. According to He *et al.*, breast and lung cancer account for 37.2% and 24.2% of pituitary metastatic lesions, respectively (10). The main particularity in LAC consists in a large spectrum of appearances and may not appear on the classical chest radiography as it was in our case (11). This should lead to further investigation with cross-sectional imaging at this stage, including basic pathology and CT imaging of the neck, chest, abdomen and pelvis (12).

We believe that metastasis to the PS may be underdiagnosed, especially given that the associated clinical symptoms are not specific and insidious.

In our case, the clinical presentation was an authentic DI. Ariel *et al.* noticed in their chart review that the presenting symptoms were mostly nonspecific, except for the common finding of polyuria that reflected an underlying DI (13). In the same study, DI was found in 50% of the cohort and many of them had clear radiographic involvement of the neuro-hypophysis or the stalk noted by frequent stalk thickening, similarly to our patient.

It is assumed by many authors that a clinical presentation made of pituitary stalk thickness with loss of posterior MRI signal is difficult to distinguish between

systemic disease from metastatic pituitary lesions based on imaging studies (14). Linking clinical characteristics with the absence of systemic clinical and biological signs help discern whether a pituitary lesion needs more thorough workup to rule out metastasis from a distant primary.

Studies, including a recent meta-analysis, indicate that DI is the most common clinical manifestation in patients with pituitary metastasis (15, 16, 17). Reports have indicated that DI is highly associated with a metastatic lesion. The anatomical explanation is that metastases target the posterior lobe of the pituitary gland and the infundibulum rather than the anterior lobe, because metastases follow the pattern of pituitary blood arteries in the neurohypophysal blood vessels (6, 14, 18). The posterior pituitary and the infundibulum are the preferential sites for metastases as they receive direct arterial blood supply from hypophyseal arteries, whereas blood supply to the anterior pituitary is mainly from the hypophyseal portal system, which is not arterial (19).

Solitary PS involvement without finding metastatic pituitary mass is an exceptional presentation. Kurkijian *et al*. have described two patients with symptomatic PS involvement from metastatic breast carcinoma (7). According to authors, we should consider searching for primary breast cancer and primary LC, since these are the most common cancers metastasizing to the PS.

The other main originality of our case is the concomitant diagnosis of both endocrinological failures, as it was initiated with a DI and followed by an acute AI. In a study including bilateral AI, 4% of patients had metastatic adrenal lesions with bilateral adrenal lesions (20). The primary cancers leading to adrenal metastases in this study included kidney, bronchogenic carcinoma and breast cancers. For patients with adrenal lesions due to malignancy, adrenal biopsy may be an accessible opportunity to diagnose the primary neoplasm. The overall sensitivity of adrenal biopsy for malignancy is of 87% with a specificity of 100% (21). Bilateral adrenal metastasis is a frequent cause of AI due to neoplastic infiltration of the adrenal glands as shown in our patient.

The combination of failure in the pituitary area and primary AI is rarely reported (8, 22). We may believe that, in our case, both adrenal and neurohypophysial failures were evolving at the same time.

Presence of distant metastases is a major factor for unfavourable prognosis in LC. Studies have shown recently that LAC patients with a single metastasis in a single organ have a significantly better life expectancy than those with more than one metastatic lesion (9). There was a clinically relevant decrease in life expectancy with the increasing number of metastatic organs. In a recent review, patients from recent studies had longer survival than others due to the improvement of therapeutics (23). Through advances in neuroimaging and oncological therapies, patients with metastases to PS are living longer and are more often discovered at early stage.

In conclusion, we reported a rare presentation of LAC revealed by a DI at first and followed by an acute AI. Pituitary metastases are well known to target the posterior pituitary. As in the presented case, patients diagnosed with DI due to PS thickness should be considered as a metastasis, after exclusion of the classical systemic and infectious diseases.

In female patients, the main cancers to be suspected are breast and lung cancers. As not every patient presents with symptoms of metastasis, there is a need to recognize the clinical syndromes associated with potential metastasis to the pituitary.

In the same way, bilateral adrenal mass should be considered as adrenal metastasis, and confirming the diagnosis by adrenal biopsy may be interesting. Additionally, in a patient with newly diagnosed bilateral adrenal mass, hormonal assays of pheochromocytoma and adrenocortical hypofunction should be performed. Screening all patients with a chest X-ray or thoracic CT for LC could lead to an early diagnosis of the neoplasm.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
A written informed consent was obtained from the patient before the beginning of the writing.

Author contribution statement
T Ach was the main writer of the manuscript. All the team members reviewed the manuscript and helped in the patient care and follow-up.

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