Diabetes insipidus as a main symptom of cancer

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Hormonal disturbances are a possible complication of malignant disease not derived primarily from the endocrine cells. They may result from paraneoplastic hormonal activity of the tumor, such as frequently described Cushing's syndrome in the course of ectopic secretion of adrenocorticotropic hormone (ACTH), a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and malignancy related hypercalcemia. Endocrinopathy may also be due to the destruction of the organ of internal secretion by the local invasion or distant tumor metastasis, such as secondary lesions in the hypothalamic-pituitary area. Thus, the clinical picture of malignancy sometimes may be dominated by the symptoms of hormonal deficiency. Diabetes insipidus (DI) is a rare complication of neoplastic disease, and its presence requires extended diagnostics.

We present two case reports of patients with metastases to the pituitary gland (MP) without an incriminating history suggesting malignancy, where DI was only the tip of the iceberg called cancer. Careful clinical evaluation and additional studies allowed the diagnosis of advanced malignancy.

A 74-year-old man with a 3-month history of polydipsia (up to 5 l/day), polyuria, nycturia and loss of appetite (without cachectic appearance) was admitted to our department with DI suspicion. Additionally he suffered from essential hypertension well controlled with amlodipine. He has been a regular smoker for 10 years. The history of malignancy and symptoms of hormonal imbalance except posterior lobe were negative. Physical examination revealed no significant abnormalities; blood pressure and heart rate were 110/70 mm Hg and 80 per minute respectively. Plain chest X-ray revealed a tumor of the right pulmonary hilus. The chest computed tomography (CT) showed a pathological mass sized 31 mm × 29 mm in one segment of the right lung with a pathological enlargement of the mediastinal lymph nodes: right paratracheal, subcarinal and aortopulmonary region (Figure 1).

Bronchofiberoscopy did not detect any tumor. For appropriate evaluation of lymphadenopathy and to obtain material for pathomorphologic diagnosis we decided to perform mediastinoscopy. The pathologically changed lymph node (group 4 according to American Thoracic Society Definitions of Regional Nodal Stations) was excised. The histopathological assessment of the lymph node revealed metastasis of squamous carcinoma. Magnetic resonance imaging (MRI) of the head with post-gadolinium enhancing identified two pathological lesions of the sellar area. One dumbbell-shaped mass was located in the intrasellar and su-

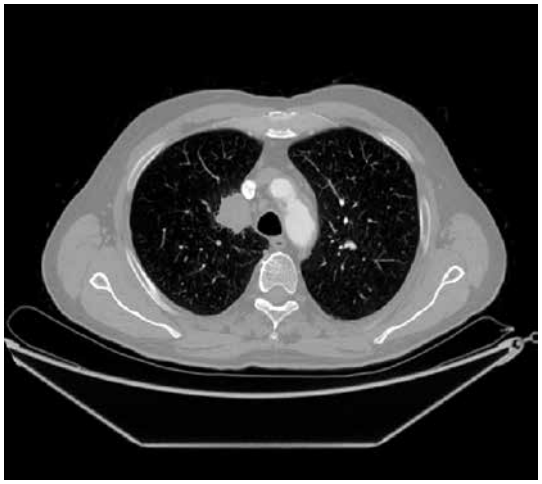

Figure 1. Chest CT: pathologic mass sized 31 mm × 29 mm in one segment of the right lung with a pathological enlargement of the mediastinal lymph nodes

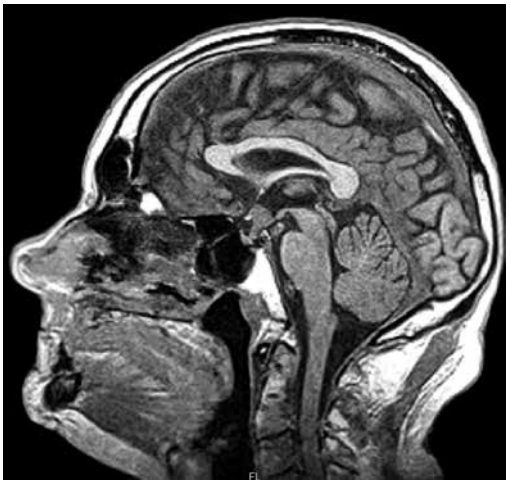

Figure 2. Head MRI: two pathological lesions of sellar area: one dumbbell-shaped mass located intrasellar and suprasellar region (10 mm × 15 mm in size) adhered to the hypothalamus and optic chiasm; the second one in the stalk of pituitary gland with 3 mm dimension

prasellar region, 10 mm × 15 mm in size, adhered to the hypothalamus and optic chiasm without penetration to the cavernous sinus. The second lesion was described in the stalk of the pituitary gland with 3 mm dimension. The anterior lobe of the pituitary gland (PG) was located at the bottom of the Turkish saddle; its height was 3 mm. There was no signal from the posterior lobe of PG (Figure 2).

The results of routine laboratory tests found no abnormalities typical of metastatic cancer disease. Observed irregularities are shown in Table I.

The results of hormonal laboratory tests suggested anterior and posterior pituitary lobe insufficiency. There was also hyperprolactinemia observed with no effect after metoclopramide (MTC) stimulation (Table II).

Taking into consideration the whole clinical picture and performed additional studies we diagnosed lung cancer, with insufficiency of anterior and posterior lobe of PG in the course of MP. The patient after oncologist consultation was qualified for chemotherapy. Endocrine substitution included adrenal axis, thyroid axis and analogue

Table I. Reported irregularities in the results of the basic laboratory research

Parameter	Result	Reference values
ESR EDTA [mm/h]	52	2–20
Uric acid [mg/dl]	8.1	3.5–7.2
Creatinine [mg/dl]	1.33	0.7–1.3
Lactate dehydrogenase [U/l]	223	125–220
Total cholesterol [mg/dl]	301	120–200
Ca 19.9 [U/ml]	48.84	< 37

ESR – erythrocyte sedimentation rate

Table II. Results of laboratory tests evaluating pituitary function

Parameter	Result	Reference values
Hormonal evaluation of anterior lobe of pituitary gland		
TSH [µU/ml]	0.18	0.34–4.94
fT4 [pmol/l]	13.21	9.01–19.05
fT3 [pmol/l]	4.08	2.63–5.7
Cortisol 8.00 a.m. [nmol/l]	175	101–536
Cortisol 8.00 p.m. [nmol/l]	36	79–478
ACTH 8.00 a.m. [pg/ml]	26.9	< 46
ACTH 8.00 p.m. [pg/ml]	26.3	(Not validated)
Cortisol (nmol/day) – urine	< 27.4	12–486
Testosterone [nmol/l]	1.62	5.4–19.5
LH [U/l]	0.25	1.14–8.75
hGH [mIU/l]	0.17	(Not validated)
IGF-1 [ng/ml]	< 25	64–188
Prolactin [mIU/l] after MTC 0' – 1841 60' – 1885 120' – 1929		108.0–557.1 (without stimulation)
Hormonal evaluation of posterior lobe of pituitary gland		
Sodium [mEq/l]	139	136–145
Potassium [mEq/l]	4.0	3.5–5.1
Serum osmolality [mOsm/l]	303	270–295
Urine osmolality [mOsm/l]	138	250–1300
Urine specific gravity [kg/l]	1.003	1018–1030

Table III. Reported irregularities in the results of the basic laboratory studies

Parameter	Result	Reference values
ESR EDTA [mm/h]	35	2–20
CRP [mg/l]	73	< 5
Total cholesterol [mg/dl]	228	120–200
Triglycerides [mg/dl]	270	< 150
GT [U/l]	65	8–61
Lactate dehydrogenase [U/l]	354	125–220
Total cholesterol [mg/dl]	228	120–200
Ca 19.9 [U/ml]	1371	< 37

GT – γ-glutamyl transpeptidase, CRP – C-reactive protein

Table IV. Results of laboratory tests evaluating pituitary function

Parameter	Result	Reference values
Evaluation of anterior lobe of pituitary gland		
TSH [µU/ml]	1.011	0.34–4.94
fT4 [pmol/l]	13.98	9.01–19.05
Cortisol 8.00 a.m. [nmol/l]	273	101–536
Cortisol 8.00 p.m. [nmol/l]	238	79–478
ACTH 8.00 a.m. [pg/ml]	43.9	< 46
ACTH 8.00 p.m. [pg/ml]	20.9	(Not validated)
Cortisol [nmol/day] – urine	215	12–486
17-OH-CS [mg/day]	7.4	2.5–7.5
17-KS [mg/day]	34.1	10–17
DHEA-S [µg/dl]	167	80–560
Androstenedione [ng/ml]	2.55	0.7–3.6
Testosterone [nmol/l]	15.2	5.76–28.14
LH [U/l]	3.42	1.80–8.16
FSH [mIU/ml]	5.68	1.37–13.58
hGH [mIU/l]	0.773	(Not validated)
IGF-1 [ng/ml]	138	64–188
Prolactin [mIU/l] at MTC 0' – 229.7 60' – 1137.4 120' – 727.4		108.0–557.1 (without stimulation)
Evaluation of posterior lobe of pituitary gland		
Sodium [mEq/l]	148	136–145
Potassium [mEq/l]	4.2	3.5–5.1
Serum osmolality [mOsm/l]	301	270–295
Urine osmolality [mOsm/l]	117	250–1300
Urine specific gravity [kg/l]	1.001	1018–1030

of vasopressin. To reduce hyperprolactinemia, resulting probably from the loss of tonic inhibitory control, we used a dopamine receptor agonist.

A 60-year-old man with 1-month history of polydipsia (up to 6 l/day), polyuria, nycturia, mild fever, loss of appetite and decrease in body weight (by 4 kg) was admitted to our department for evaluation of DI. Medical history revealed no other chronic diseases, but long-term cigarette smoking (38 years). The patient was operated on three times: 1969 – appendectomy due to appendicitis; 1973 – Billroth I gastrectomy because of peptic ulcer disease complication; and 1998 – cholecystectomy due to cholelithiasis. Physical examination revealed supraclavicular lymphadenopathy, flushing of the face and neck with a small swelling; blood pressure was 130/90 mm Hg and heart rate 90/min. Basic laboratory studies showed high lactate dehydrogenase activity and elevated tumor marker CA 19.9 concentration (Table III). Hormonal tests for pituitary function revealed only features of posterior lobe insufficiency (Table IV).

The ultrasound of the supraclavicular region confirmed the presence of bilateral placed hypoechoic clusters of lymph nodes with the largest dimension 12 mm. The chest CT showed a large number of lymph node packets located in the retrosternal, aorto-pulmonary window, right paratracheal, and posterior mediastinum. Unequivocal focal lesions in the lungs were not established (Figure 3).

The imaging studies – chest X-ray, CT of abdomen with small pelvis, gastroduodenoscopy, colonoscopy (due to anatomical conditions hepatic flexure of colon was reached only), bronchofiberoscopy – and otolaryngological examination revealed no features of cancer. For further lymph node enlargement evaluation right scalene biopsy was performed. The result of the histopathological assessment was squamous cancer. Magnetic resonance imaging with contrast enhancement of the head identified a pathological mass located on the border between the anterior and posterior pituitary lobe, 8 mm × 7 mm dimension. The tumor was hypointense in the T1-weighted and poorly grasped in T2-weighted images. Also thickening of the pituitary stalk to 5 mm was observed (Figure 4).

Disseminated squamous cell carcinoma with likely primary lesion from the lungs and MP with symptoms of DI were diagnosed. Due to the risk of superior vena cava syndrome, the patient was treated with radiotherapy to the mediastinum and surrounding supraclavicular area. Later he was qualified for chemotherapy. The patient also re-

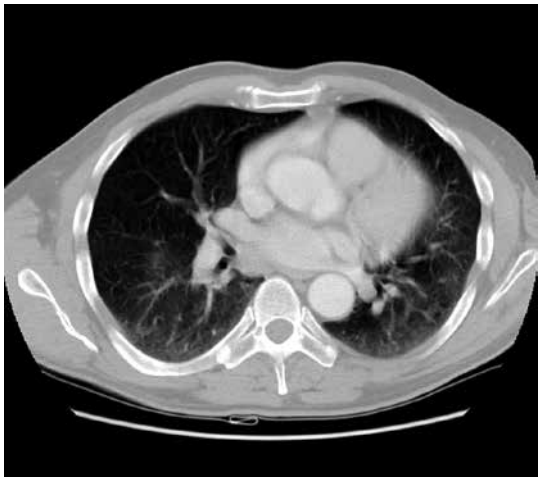

Figure 3. Chest CT: large number of lymph nodes packets located in retrosternal, aorto-pulmonary window, right paratracheal and posterior mediastinum

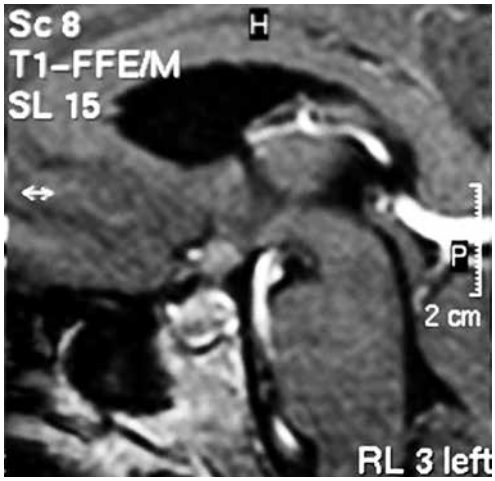

Figure 4. Head MRI: pathological mass located on the border between anterior and posterior pituitary lobe (8 mm × 7 mm dimension) and thickening of the pituitary stalk to 5 mm

ceived symptomatic treatment of DI with a vasopressin analogue. After 3 months and 3 cycles of chemotherapy the patient was admitted to our department due to significant deterioration in general condition. In additional studies an enlarged right pulmonary hilus was found, as well as liver metastases and further increase of the infiltration of the pituitary stalk, with stable diameter of the lesion within the pituitary gland. Based on performed laboratory tests the complete insufficiency of the anterior lobe of the pituitary gland was identified. The treatment included substitution of thyroid and adrenal axis. Temporary improvement of general state was obtained. During hospital stay, the patient developed acute coronary syndrome, eventually complicated with circulatory-respiratory failure and died.

Metastasis to the pituitary gland (MP) is a rare clinical problem among patients with cancer disease. According to the literature, its incidence is estimated at 1–3.6% of patients with cancer disease undergoing autopsy [1] and represents less than 1% of all pituitary tumors treated with neurosurgery [2–4]. Breast and lung cancer are the most common malignancies giving MP [4–11]. Occasionally, MP were also reported in hematological, thyroid, kidney, colon, prostate, bladder, stomach, liver [12], ovarian cancer [13] and germinoma [14]. It is estimated that 70% of MP derives from breast in women and 60% of MP originate from lungs in men [15].

The presence of MP may complicate the course of cancer at every stage of disease [4, 9]. It may be the first and only manifestation of neoplastic disease. Mostly, presence of metastatic lesions concerns the posterior lobe, rather than the two lobes simultaneously or only the anterior one [4, 9, 16, 17]. Predilection for the posterior lobe is explained by its direct blood supply from the circulatory system and the adhesion of the dura mater on a wider area. Most MP are asymptomatic in course; clinically overt cases concern only approximately 2.5–18.2% of patients [4, 6, 15, 18, 19]. The most typical symptoms of MP include a short history for DI, ophthalmoplegia and headache [4, 9, 15, 16, 18, 20, 21]. The percentage of DI cases caused by MP among all DI cases is estimated as 14% [15]. The symptoms of anterior lobe dysfunction are less specific for MP, as they often are masked by the essential signs of malignancy. In one analysis of patients with MP, symptoms of anterior lobe insufficiency without DI were estimated in 15% [4]. Further more detailed studies using sensitive laboratory tests and imaging techniques indicate a higher incidence of anterior lobe hypopituitarism [18].

To make a diagnose of MP is particularly difficult in patients without evidence of malignant disease. Diabetes insipidus should be taken into consideration as a hallmark of MP, which is a rare complication of benign tumor of the pituitary gland and it occurs in approximately 1% of adenomas [9]. In these cases, it is a late manifestation of the adenoma lesion. Diabetes insipidus in symptomatic patients with MP is calculated as 60–70% [4, 9]. Imaging techniques of the central nervous system (CNS) such as MRI or CT to a lesser degree differentiate primary and secondary tumors of the pituitary gland. The best radiological signs of MP include presence of metastatic lesions in another location of the CNS, infiltration of surrounding structures close to the Turkish saddle and suprasellar spread of the tumor with its dumbbell-shaped picture [18, 20, 22].

The treatment of patients with MP is usually palliative, with the choice of radiotherapy applied

to the surrounding of the pituitary gland and/or chemotherapy. None of these methods affect the survival of patients. Neurosurgical treatment is rarely used because of cancer advance. Neurosurgery is considered only among patients with a vague image of the tumor or people with neurological symptoms, especially because of the possible cranial nerve damage [4, 9]. A bad prognosis largely depends on the end stage of cancer disease rather than direct connection with MP. Median survival is determined as 6–7 months [9].

In conclusion, we presented cases of 2 patients where DI was the main symptom of oncological disease not diagnosed earlier. Suspicion of malignancy in patient 1 was established thanks to positive lateral chest X-ray, where a centrally located tumor was found. In patient 2, typical physical examination suggested malicious lymph node enlargement. Conjecture of MP was based on clinical and radiological assessment. In both cases the water-deprivation test was not performed due to the clear clinical picture of DI and the presence of a pathological mass in MRI. Similarly to the available medical literature, we did not confirm the histopathological nature of the MP. Local advancement of the disease *per se* disqualified the patients from radical treatment. Noteworthy is the lack of clinical signs and symptoms of hypopituitarism in patient 1 and the rapid development of anterior lobe insufficiency confirmed in laboratory studies in patient 2.

Our two cases are distinct examples of the fact that DI may only be the tip of the iceberg. Physicians, especially endocrinologists and GPs, should remember that DI may be the first and only manifestation of malignancy. Moreover, administration of vasopressin analogues will improve patients' quality of life and in selected cases (e.g. thyroid cancer, lymphoma) early diagnosis may also affect survival.

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