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Hypopituitarism in a patient with breast cancer

Niedoczynność przysadki u pacjentki z rakiem piersi

Introduction

The pituitary gland is a critical organ of the endocrine system affecting many physiologic processes, including maintenance of metabolic, fluid, and electrolyte homeostasis; regulation of cellular production and growth [Johnstone et al., 2014]. Hypopituitarism is a condition in which a deficiency is present in hormones produced by the pituitary gland, ranging from a single hormone to all hormones (termed panhypopituitarism). Depending on hormones which are affected, clinical manifestations have a range of severity; most often, presentation is nonspecific and vague. Clinical manifestations of hypopituitarism can include amenorrhea, decreased muscle mass, increased visceral fat, fatigue, dizziness, nausea, vomiting, hypotension, hypoglycemia, polyuria, and polydipsia [Kim et al., 2015]. Hypopituitarism is thought to be an uncommon condition with a prevalence of ~46 per 100,000 [Higham et al., 2016] without differences related to sex. It can be due to a variety of tumoral, inflammatory, or infiltrative lesions or trauma or radiation of the hypothalamic–pituitary region, with the most common cause represented by non-functioning pituitary macroadenomas [Pekic et al., 2017]. It has been recognized that hypopituitarism in the elderly is an underestimated condition [Foppiani et al., 2008]. Its symptoms can be attributed to ageing or to associated comorbidities and the possible effects of drugs used for the treatment of comorbidities must be taken

into account. All these peculiarities must be considered for a correct diagnostic and therapeutic approach. In this article we report the patient with hypopituitarism related to the past history of breast cancer and its treatment.

Methods: Case report

The 83-year-old woman, with a history of malignant neoplasm of her breast, underwent local tumour excision, chemotherapy, and radiotherapy, and was treated for an anterior wall myocardial infarction with PTCA LAD (percutaneous coronary angioplasty, left anterior descending) and stent implantation; she also received post-surgical treatment for retinal detachment (2004), and has hypertension, type 2 diabetes, and paroxysmal atrial fibrillation.

The patient was diagnosed with breast cancer in 2021 and underwent local excision of the lesion. Prior to initiating treatment, the patient was consulted with a cardio-oncologist due to cardiac comorbidities. Enhanced cardiac monitoring was recommended during oncological therapy. In February 2022, the patient underwent immunochemotherapy according to the PXL+Herceptin protocol (Paclitaxel), with good early tolerance.

She was admitted to the internal medicine ward due to nausea, weakness, and muscle pain persisting for a week, along with weight loss. The patient did not report vomiting or abdominal pain. Two weeks earlier, she had completed a course of antibiotics for a urinary tract infection. Upon hospital admission, the physical examination revealed the patient to be in fair overall condition and fully alert and oriented. The patient reported no allergies. The heart rate (HR) was 70 bpm, blood pressure (BP) 160/75 mmHg, respiratory rate (RR) 16 breaths per minute, oxygen saturation (SpO2) 98%, temperature (T) 36.5°C. The patient had clear lung sounds, no wheezing or crackles. The patient's abdominal examination revealed a soft, non-tender abdomen with normal bowel sounds. Apart from that, the physical examination revealed cold hands, and pale, dry skin. Routine blood tests showed hyponatremia 116 mmol/l (Table 1). During hospitalisation, the patient's serum sodium levels were being gradually corrected with an intravenous 0.9% NaCl solution (Figure 1). An abdominal ultrasound was performed, revealing bilateral calculi at the ureterovesical junction. A urology consultation was recommended, and the patient was scheduled for bilateral URS-L (UreteroRenoScopic Lithotripsy) on an elective basis. Based on the patient's symptoms, hormonal diagnostics were ordered. Tests of thyroid function, adrenocorticotropic hormone (ACTH), cortisol, the gonadotropins follicle stimulating hormone (FSH), prolactin and luteinizing hormone (LH) were commissioned too. The results showed normal TSH (thyroid stymulating hormone) and ACTH levels, and decreased levels of FSH (follicle stimulating hormone), FT3 (free triiodothyronine), FT4 (free thyroxine), and LH (luteinizing

Tab. 1. *Laboratory findings related to hypopituitarism in a patient*

Hospital day	Laboratory finding		Normal range of value
	Test	Result	
Day 1	Serum sodium	116 mmol/l	136–145 LL
	Urine osmolality	220 mOsm/kg	50–1400
	Serum osmolality	253 mOsm/kg	270–295 L
Day 2	ACTH	18,3 pg/ml	7,2–63,3
	TSH	1,28 ulU/ml	0,27–4,20
	FT3	1,71 pg/ml	2,02–4,43 L
	FT4	0,51 ng/dl	0,93–1,70 L
	Serum cortisol (time 8:00)	11,5 ug/dl	3,7- 19,4
	Serum sodium	120 mmol/l	136–145 L
	Urine osmolality	260 mOsm/kg	50–1400
Day 5	TSH	1,75 ulU/ml	0,27–4,20
	FT3	1,82 pg/ml	2,02–4,43 L
	FT4	0,54 ng/dl	0,93–1,70 L
	Serum sodium	127 mmol/l	136–145 L
	Serum osmolality	266 mOsm/kg	270–295 L
Day 6	TSH	1,55 ulU/ml	0,27–4,20
	FSH	3,8 mlU/ml	25,8–134,8 L after menopause
	FT3	1,68 pg/ml	2,02–4,43 L
	FT4	0,51 ng/dl	0,93–1,70 L
	LH	0,7 mlU/ml	7,7–58,5 L after menopause
	Serum calcium	4,68 mEq/l	4,30–5,20
	Serum sodium	129 mmol/l	136–145 L
	Serum osmolality	285 mOsm/kg	270–295
	Prolactin	10,4 ng/ml	4,8–23,3
Day 7	Serum sodium	135 mmol/l	136–145 L
Day 8	Serum sodium	136 mmol/l	136–145

ACTH – adrenocorticotropic hormone; FSH – follicle-stimulating hormone; LH – luteinizing hormone; TSH – thyroid-stimulating hormone; FT3 – free triiodothyronine; FT4 – free thyroxine

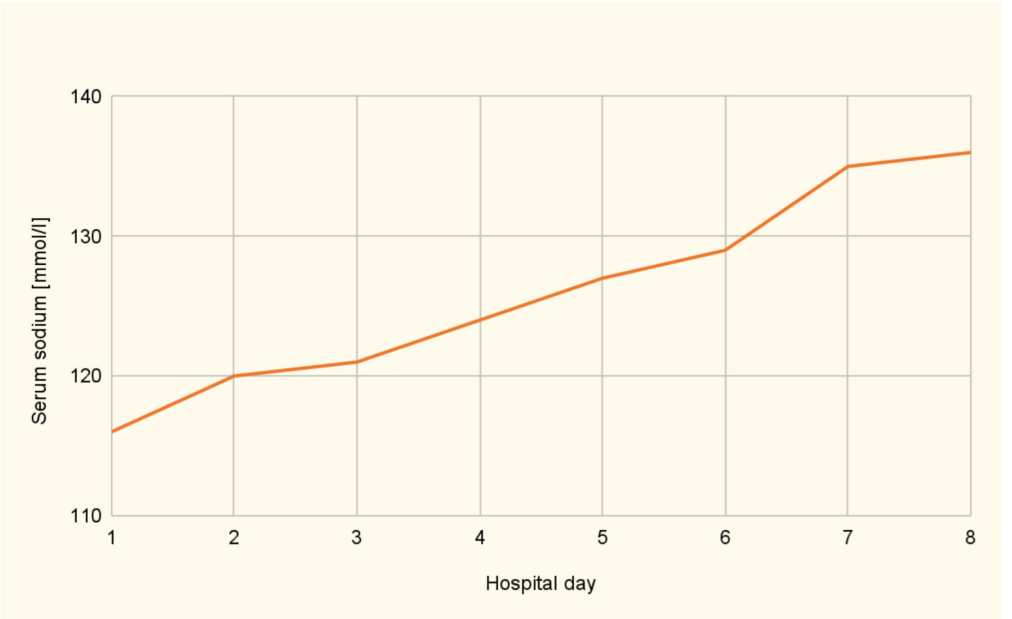

Fig. 1. *Serum sodium progression*

hormone), with secondary hypofunction of the peripheral glands (Table 1). The results indicated hypopituitarism. The patient did not consent to an MRI (magnetic resonance imaging) examination due to claustrophobia. CT (computed tomography) head scan was performed, and no areas of contrast enhancement in the brain were found. Approximate dimensions of the pituitary gland were as follows: anteroposterior (AP) 11 mm, craniocaudal (CC) 7 mm, and transverse (TR) 7 mm.

During hospitalisation, the patient underwent an ophthalmologic consultation to assess the visual fields of both eyes due to suspected pituitary gland changes. The examination found no damage to the optic pathways. An arcuate scotoma in the upper visual field of the right eye was detected, while the left eye remained unchanged. The visual field defect was a consequence of vitrectomy. Combining the symptoms and examinations, the diagnosis of hypopituitarism was considered.

The patient in a condition appropriate for her comorbidities, was discharged home with recommendations to perform hormonal panel tests in 6 weeks. A referral to the Endocrinology Clinic was provided. The following treatment was prescribed: Zinnat 250 mg (for 5 days), Enterol (for 5 days), Hydrocortisone-SF 10 mg, Euthyrox N 50 µg, and Canephron N 3x5 ml (for 3 weeks after completing the antibiotic treatment).

Discussion

Hypopituitarism is defined as deficiency or complete loss of isolated or combined pituitary hormones. Symptoms vary depending on the number of affected hormones, age of onset, the cause of the disease and severity of deficiency [Chung et al., 2022]. The deficiency can affect both anterior and posterior lobe, leading to lack of such hormones as growth hormone (GH), FSH and LH, ACTH, TSH, prolactin (PRL), oxytocin (OXT) and antidiuretic hormone (ADH) [Higham et al., 2016].

As it was mentioned, symptoms result from various factors, including the number of hormones affected, therefore they depend on hormonal axes malfunction. Noticeable changes in a physical examination include: a small and soft thyroid gland, cold, dry and coarse skin, alopecia and hair thinning, non-pitting type edema and delayed tendon reflexes in hypothyroidism, postural hypotension and fatigue in hypoadrenalism, loss of axillary and pubic hair in women and small and atrophic testes in men in hypogonadism, hypernatremia, polyuria and diluted urine in arginine vasopressin resistance (diabetes insipidus) and, when neurological and ophthalmic involvement occurs, there are cases of loss of visual acuity, extraocular paresis and bitemporal hemianopsia and others, depending on the regulatory pathway affected [Chung et al., 2022, Gounden et al., 2024].

There are various causes of hypopituitarism: congenital (isolated or multiple pituitary hormone deficiency), neoplastic (pituitary adenoma, peri-pituitary tumours), vascular (infarction/haemorrhage), immunological, infectious, post-irradiation or miscellaneous [Chung et al., 2022]. From the clinical perspective, the condition can be divided into acute and chronic hypopituitarism, with the first carrying a serious risk of mortality, in most cases secondary to ACTH loss and subsequent hypoadrenalism [Higham et al., 2016]. Out of the causes of hypopituitarism, there are at least two that may specifically underlie our patient's condition.

Immunological (or inflammatory/infiltrative) causes lead to the condition known as hypophysis, which can be granulomatous, lymphocytic, xanthomatous, necrotizing, immunotherapy-induced (inhibitors of CTLA-4), IgG4-related or caused by giant cell granuloma, hemochromatosis, granulomatosis with polyangiitis (GPA), sarcoidosis or Langerhans cell histiocytosis [Chung et al., 2022].

Cancers and neoplasms affecting the pituitary gland include pituitary adenoma and peri-pituitary tumours, such as Rathke's cleft cyst, craniopharyngioma, non-adenomatous neoplasms (meningioma, glioma, germ cell tumour), and secondary tumours (metastases), especially breast, renal and bronchus [Chung et al., 2022]. Breast cancer metastasizes to the pituitary gland quite frequently. Pituitary metastases are detected in between 6 and 8% of breast cancer patients [Fassett et al., 2004]. The most common

clinical manifestation of metastatic tumour of the pituitary is diabetes insipidus, because the anterior pituitary lobe has no direct blood supply, hence its involvement happens through the spread from the posterior lobe [Gunawardena et al., 2016].

There are numerous reports of breast-metastases-induced hypopituitarism [Sturm et al., 2004, Fortunati et al., 2015, Oueslati et al., 2021]. Authors suggest the condition is rather difficult to diagnose due to nonspecific symptoms and the presence of nerve palsies and visual deficiencies indicate the metastatic nature of hypopituitarism [Oueslati et al., 2021]. Our patient was diagnosed with right breast cancer in October 2021 and underwent operational treatment (breast conserving therapy (BCT) and sentinel lymph node biopsy (SLNB) in November 2021, with metastases detected in 3 of 6 dissected lymph nodes. In December 2021, the patient underwent axillary lymphadenectomy, with metastases in 2 of 10 lymph nodes. The patient started chemo- and immunotherapy with PXL and Trastuzumab (Herceptin) in February 2022, with Herceptin therapy lasting until February 2023. The patient additionally received radiotherapy for the right breast and hormonal therapy with Letrozole (Aromek).

Three years after cancer diagnosis and over a year after the end of Herceptin treatment, the patient was admitted to the hospital, suffering from fatigue, nausea, muscles pain and hyponatremia (116 mmol/l) (Table 1). These symptoms are typical for hypoadrenalism. Moreover, laboratory tests carried out at our hospital indicated decreased levels of free thyroid hormones with TSH within the normal range, and decreased levels of LH and FSH with secondary hypoactivity of peripheral glands (Table 1). These data are consistent with other described cases of hypopituitarism in patients with breast cancer, where patients suffered from panhypopituitarism [Sturm et al., 2004] or combined hypopituitarism [Fortunati et al., 2015, Oueslati et al., 2021].

As we mentioned above, there are at least two possible causes of hypopituitarism in our patient. First of all, her basic condition, which is breast cancer. Metastatic lymph nodes were detected both during SLNB and axillary lymphadenectomy, which suggests that further metastases are possible. To check for the possibility of metastasis to the pituitary gland, the patient was offered an MRI; however, she refused due to claustrophobia. Instead, a CT scan was proposed, and she agreed. The results showed no enhancement within the encephalon, and the pituitary dimensions were AP 11mm, CC 7mm, and TR 11mm. However, it is worth noting that MRI is considered a superior method for radiological diagnostics of the pituitary gland, as it has excellent soft tissue contrast, which allows for diligent evaluation of intracranial structures. MRI provides a detailed depiction of the pituitary anatomy and its relationships with local structures, allowing for the detection of micro-alterations in its architecture. CT has lower soft tissue resolution compared with MRI but can be helpful in detecting calcifications, abnormalities in bones, or surgically relevant bony anatomy [Varrassi et al., 2019]. Moreover, MRI

is better at visualising the posterior lobe and pituitary stalk and is superior in detecting the cystic nature of tumours [Guy et al., 1991].

A question arises, whether it is possible that the CT simply did not show the metastasis in the pituitary gland, which could have been detected in MRI? It might be one of the explanations of our patient's current condition.

A second possibility we consider is hypophysitis due to breast cancer immunotherapy. There is a link between usage of a cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor, a IgG1 monoclonal antibody against CTLA-4, called Ipilimumab [Chung et al., 2022, Iwama et al., 2014, Caturegli et al., 2016]. Secondary hypophysitis has been reported in 10–15% of patients treated with Ipilimumab. This drug is used mostly against metastatic melanoma [Chung et al., 2022]. Our patient underwent therapy with Herceptin (Trastuzumab), a monoclonal IgG1 antibody against human epidermal growth factor receptor 2 (HER2), therefore it is employed in HER2+ breast cancer therapy. There is well-described evidence of Trastuzumab-induced cardiotoxicity [Copeland-Halperin et al., 2019], yet there seem to be no data regarding its activity on the pituitary gland. Nevertheless, HER2 expression has been reported in primary pituitary tumours, such as prolactinomas, leading to an increase of MEK/ERK signalling pathway activity in those tumours. This pathway plays a central role in regulation of cell proliferation, differentiation and survival [Petiti et a;., 2018]. In addition, it has been proven that HER2+ breast cancer metastases, whether in lymph nodes or further disseminated, retain expression of HER2+ on their surface [Carlsson et al., 2004].

Conclusions

Summarising, there is a possibility that the female patient's hypopituitarism is a result of HER2+ breast cancer metastasis and/or its treatment. We would suggest trying to encourage the patient to overcome claustrophobia and undergo a MRI scan. Basic blood tests evaluating the pituitary function should be performed to investigate affected axes (adrenocortical, thyroid and gonadal), including measurement of serum levels of prolactin, insulin-like growth factor-1, growth hormone and paired plasma and urine osmolality (some of which were conducted – Table 1). It is also recommended to conduct dynamic tests (stimulation tests, such as insulin tolerance test, glucagon, arginine, assessing the hypothalamic-pituitary unit and TRH, GnRH, GHRH tests, which directly stimulate the anterior pituitary lobe with synthetic hypothalamic peptides, allowing measurement of the pituitary hormone response) to further support the diagnosis [Chung et al., 2022, Gounden et al., 2024].

Conflict of interest:

All authors declare that they have no conflicts of interest.

Abbreviations:

ACTH *(adrenocorticotropic h*ormo*ne)*; **ADH** (*antidiuretic hormone*); **AP** *(anteroposterior)*; **BCT** *(breast conserving therapy)*; **BP** *(blood pressure)*; **CC** *(craniocaudal)*; **CT** *(computed tomography)*; **CTLA-4** *(cytotoxic T-lymphocyte antigen-4)*; **ERK** *(extracellular signal regulated kinas)*; **FSH** *(follicle stimulating hormone)*; **FT3** *(free triiodothyronine*); **FT4** *(free thyroxine)*; **GH** *(growth hormone)*; **GHRH** *(growth hormone-releasing hormone)*; **GnRH** *(gonadotropin-releasing hormone)*; **GPA** *(granulomatosis with polyangiitis)*; **HER2** *(Human epidermal growth factor receptor 2)*; **HR** (*heart rate)*; **LAD** *(left anterior descending)*; **LH** *(luteinizing hormone)*; **MEK** *(miogen-activated protein)*; **MRI** *(magnetic resonance imaging*); **OXT** *(oxytocin)*; **PRL** *(prolactin)*; **PTCA** *(percutaneous coronary angioplast)*; **PXL** *(Paclitaxel)*; **RR** *(respiratory rate)*; **SLNB** (*sentinel lymph node biopsy)*; **SpO2** *(oxygen saturation)*; **T** *(temperature)*; **TR** *(transverse)*; **TSH** *(thyroid stymulating hormone)*; **URS-L** *(UreteroRenoScopic Lithotripsy)*.

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Abstract:

Aim: This article discusses a case study of an 83-year-old woman with a history of malignant breast cancer, who was admitted to the internal disease department. **Methods:** Case study **Discussion:** Patient presented weakness, nausea and muscle pain persisting for a week. Neither did the patient report vomiting nor abdominal pain. She was conscious. Combining these clinical symptoms and examinations, a diagnosis was made that the patient was suffering from hypoosmotic hyponatremia. This prompted further investigation, resulting in the discovery of probable hypopituitarism. **Conclusion:** This case underscores that the basic condition, which is breast cancer, and the therapy of breast cancer may lead to hypopituitarism, which causes severe hyponatremia.

Keywords: hypopituitarism, hormone, breast cancer, oncology, case report

Streszczenie:

Cel: W artykule omówiono przypadek 83-letniej kobiety z przebytym nowotworem złośliwym piersi, przyjętej na oddział chorób wewnętrznych. **Metody:** Studium przypadku. **Dyskusja:** Pacjentka zgłaszała osłabienie, nudności i ból mięśni utrzymujący się przez tydzień. Nie zgłaszała wymiotów ani bólów brzucha. Była przytomna. Na podstawie objawów klinicznych i badań rozpoznano hiponatremię hipoosmotyczną.

To skłoniło do pogłębienia diagnostyki, na podstawie której wysnuto podejrzenie niedoczynności przysadki mózgowej. **Wnioski:** Przypadek ten pokazuje, że podstawowa choroba jaką był rak piersi, oraz jej leczenie może prowadzić do niedoczynności przysadki a w konsekwencji do ciężkiej hiponatremi.

Słowa kluczowe: niedoczynność przysadki, hormony, rak piersi, onkologia, opis przypadku