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CASE REPORT

Hypopituitarism and goitre as endocrine manifestation of Langerhans cell histiocytosis (LCH)

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Abstract

Langerhans cell histiocytosis (LCH) in adults is a rare disorder of unknown etiology characterized by monoclonal proliferation of Langerhans cells. It belongs to dendritic cell disorders and occurs in 1–2 adults per million. The most common endocrine manifestation of classical LCH is associated with the posterior pituitary, with clinical symptoms of diabetes insipidus. Less than 80 reported cases of LCH involving the thyroid gland have been published so far.

We present the case of a 39 years old woman with 10 years history of diabetes insipidus and secondary amenorrhoea, which appeared after second delivery. She was suspected for lymphocytic inflammation of pituitary and she was administered steroid treatment. She was also treated symptomatically with desmopressin, L-thyroxine, estrogen and progestagen replacement therapy due to diabetes insipidus, secondary hypothyroidism and hypogonadotropic hypogonadism. In September 2014, she noticed a painless, firm tumour of the neck. Ultrasound (US) examination demonstrated bilateral, solid, hypoechogenic thyroid nodules. The result of fine-needle aspiration biopsy (FNAB) was not diagnostic. Due to rapid progression and US image of the tumour, she was referred for surgery. In postoperative histopathology tumour cells were positive for CD1a and S-100 protein, therefore diagnosis of LCH was established. Postoperatively, the results of thoracic computed tomography scan, abdominal US and bone scintigraphy revealed no evidence of multifocal disease. We have not observed any disease recurrence in the patient after a year of follow-up in postoperative course. This case illustrates diagnostic and therapeutic difficulties in patient with LCH.

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disorder of unknown etiology associated with monoclonal histiocytic proliferation (Arico *et al.* 2003). It belongs to dendritic cell disorders. Diagnosis is based on the result of immunohistochemical reactivity of histiocytes to CD1a and/or S-100 protein (Howarth *et al.* 1999). In adults LCH is less frequent than in children, it occurs in 1–2 adults per million. LCH has numerous clinical forms that affect different systems or different sites in the same system with variable outcomes. The frequent localisations of LCH in adults are lungs and bones. Depending on the extent and localisation of the disease at the time of evaluation, LCH can be classified as single system LCH – when only one organ/system is involved or multisystem LCH – when two or more organs/systems are affected (Minkov *et al.* 2009). Currently, there is no standard treatment for LCH. The age, extent of disease and function of vital organs are major factors helping in choosing of the therapy. The strongest arguments for chemiotherapy are in case of multisystem LCH (Minkov *et al.* 2009). The most common endocrine presentation of classical LCH is associated with the posterior pituitary, with typical symptoms of diabetes insipidus (Kaltsas *et al.* 2000, Garcia Gallo *et al.* 2010). Other frequent manifestations are secondary amenorrhea and anterior pituitary deficiency. The thyroid is rarely affected by LCH, less than 80 cases of LCH involving the thyroid gland have been published so far and the coexistence of histiocytosis in the thyroid and pituitary were reported about 25 times (Patten *et al.* 2012). Since thyroid localization of disease is infrequent, optimal management is not established.

CASE REPORT

A 39-year-old woman was admitted for follow up visit into Department of Endocrinology and Metabolic Diseases. She had been suffering from central diabetes insipidus and multihormonal anterior pituitary deficiency (hypogonadotropic hypogonadism, secondary hypothyroidism, deficiency of GH) for 10 years. Initial symptoms included polyuria, polydypsia and secondary amenorrhea, which appeared for the first time three months after the second delivery in December 2005 (Table 1). In January 2006 endocrine diagnostics of pituitary function was performed. The water deprivation test was performed for differential diagnosis of polydipsia and polyuria (9000 ml/24 h). At admission, serum osmolality at admission was 293 mOsm/kg and urine osmolality was 94 mOsm/kg. After 8 hours of water deprivation, serum osmolality reached 302 mOsm/kg and urine osmolality did not raise. After desmopressin urine osmolality markedly increased to 630 mOsm/kg, volume of urine reduced to 1600 ml and a diagnosis of diabetes insipidus was confirmed. For diagnosis of secondary amenorrhea test with LH-RH was carried out (Table 2). Normal stimulation of LH and FSH indicated hypothalamic cause of amenorrhoea. Low IGF-1 and no stimulation of GH after glucagon confirmed deficiency of GH (Table 3). Low levels of FT4 and FT3 reflected secondary hypothyroidism. Normal concentrations of cortisol and ACTH, and proper stimulation of ACTH and cortisol after glucagon indicated normal function of hypothalamus-pituitary-adrenal axis. In magnetic resonance imaging (MRI), absence of the posterior pituitary hyperintensivity and thickened pituitary stalk were observed, anterior lobe of pituitary was homo-

Tab. 1. Hormonal results of patient on admission in 2006 and 2014 years.

Hormone	Years		Reference range
	2006	2014	
TSH [mU/L]	0.21	0.54 (LT4)	0.27–4.2
Free T4 [ng/dL]	0.68	1.24 (LT4)	0.71–1.85
Free T3 [pg/mL]	1.63	2.27 (LT4)	1.8–4.6
LH [IU/L]	3.52	3.44	1.7–8.6
FSH [IU/L]	4.64	4.53	1.5–12.4
Estradiol [pg/mL]	82.145	49.2	Early follicular: 24.5–195.0 Luteal: 40.0–261.0 Postmenopausal: <10.0–39.5
IGF-1 [ng/mL]	103	82	117–329
Cortisol 8 am [µg/dL]	20.4	24.05	6.2–19.4
ACTH [pg/mL]	84.6	62	10–60
Prolactin [ng/mL]	36	13	3.4–24.1
ATg [U/mL]	<20	<20	<40
ATPO [U/mL]	38	16	<35
Osmolality of urine [mOsmol/kg H_2O]	93	460	500–800
Osmolality of plasma [mOsmol/kg H_2O]	294	279	275–295

Tab. 2. Result of LH-RH test (100 µg, *i.v.*).

	0`	30`	60`
LH [IU/L]	4.43	8.62	9.43
FSH [IU/L]	4.48	24.0	21.7

Tab. 3. Results of glucagon stimulation test (30 µg/kg b.w., *i.m.*).

	0′	60′	90′	120`	150`	180`
GH [ng/mL]	0.09	0.10	0.45	1.97	0.68	0.29
ACTH [pg/mL]	62	16.7	21.0	29.3	35.4	43.1
Corisol [µg/dL]	27.8	24.4	24.0	29.6	39.1	36.3
Glucose [mg/dL]	79	148	121	102	81	69

genic (Figures 1 and 2). Because she was suspected for lymphocytic inflammation of pituitary, she was administered steroid treatment (2006 – initially prednisone orally, then metylprednisolon intravenously and finally – prednisone in high doses). Normal pituitary function was not restored, but the therapy with steroids was complicated by weight excess, glucose intolerance and hypertension.

At admission to the Department of Endocrinology and Metabolic Diseases in September 2014 her treatment included: desmopressin (Minirin Melt 120 μg 2×1 tabl) for diabetes insipidus; estrogen and progestagen replacement therapy for hypogonadotropic hypogonadism; L-thyroxine (Euthyrox, 150 μg/daily) due to secondary hypothyroidism; valsartan, 160 mg – for hypertension; bisoprolol, 10 mg – for tachycardia, atorvastatin, 20 mg – for hyperlipidemia, metformin (850 mg 2×1 tabl) for glucose intolerance and insulin resistance. The patient did not need replacement therapy with hydrocortisone.

On physical examination, the patient appeared markedly obese. Her height was 169 cm and her body mass was 114 kg (BMI: 39.91 kg/m^2). Blood pressure was 140/90 mm Hg, and pulse rate was 88/min. The firm, painless nodule of right thyroid lobe (diameter 3 cm) was found, no lymph nodes were palpable. Lung sounds were clear at auscultation. Neurologic examination revealed normal motor and sensory functions. The results of other physical examinations were unremarkable.

Blood cell count, urinalysis, serum chemistry, and electrolytes (Na, K) were within the normal range. Values of pituitary and thyroid hormones concentrations, are shown in Table 1.

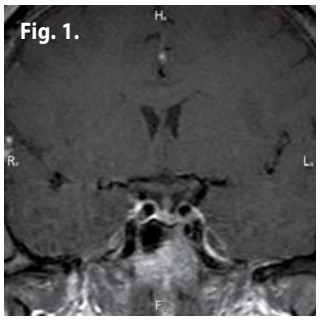
In ultrasound (US) examination irregular, bilateral, solid, hypoechogenic thyroid nodules (Figures 3 and 4), with no increased vascularity and no calcifications were revealed. The biggest tumour was located in right lobe and it was taller-than-wide (26×19×30 mm), with blurred margins. There were no enlarged or pathologic lymph nodules. Fine-needle aspiration biopsy (FNAB) was not diagnostic; non-epithelial cells with the appearance of macrophages and few lymphocytes were revealed (Figure 5).

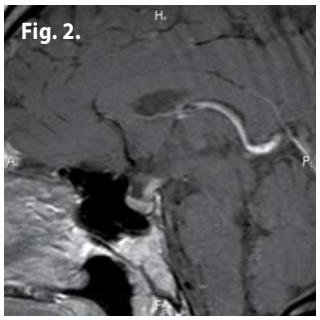
Due to the size of tumour and its high risk US image, as well as an ambiguous result of biopsy she was referred for surgery. Total thyroidectomy was performed. Postoperative course was normal, without complications (normal voice and parathyroid activity). Since in postoperative histopathology tumour cells were positive for CD1a (Figure 6) and S-100 protein diagnosis of LCH was established. Other immunohistochemical staining for TTF-1, cytokeratin 19, thyroglobulin, chromogranin, SMA, Melan A, CD138, CD3, CD20 CD15 were negative. After thyroidectomy she required the increased dose of L-thyroxine (175 μg/daily).

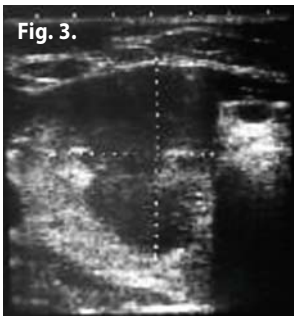
Postoperatively, the results of thoracic computed tomography scan, abdominal US, bone scintigraphy revealed no evidence of multifocal disease. We have not observed tumour recurrence in the patient after a year of follow-up in postoperative course.

DISCUSSION

We presented a case report of adult multisystem LCH with endocrine presentation – primary in the pituitary and secondary in the thyroid gland. Diagnostics, as well as the treatment of our patient faced many difficulties. Proper diagnosis was established late. Although, diabetes insipidus is reported to be the most common and well described manifestation of hypothalamic-pituitary involvement (up to 50%) (Kaltsas *et al.* 2000), however, LCH is not the only reason of diabetes insipidus. Beginning of the disease after delivery suggested diagnosis of lymphocytic hypophysitis, however personal history of other autoimmune diseases was negative. Radiological manifestations of LCH included thickening of the pituitary stalk >3 mm, loss of physiological hyperintense signal in the posterior pituitary on T1W images. LCH of pituitary has been confused with other pathologies causing thickening of pituitary stalk; Wegener's hypophysitis, sarcoidosis, germ cell tumour (de Pinho *et al.* 2010) and limfocytic hypophysitis (Lu *et al.* 2009) and may be challenging, especially when







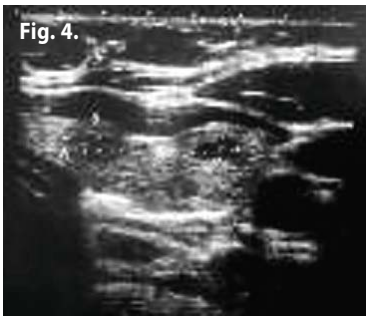


Fig. 1. Sagittal view of brain MRI – thickening of the pituitary stalk.
Fig. 2. Coronal view of brain MRI – thickening of the pituitary stalk, absence of posterior pituitary hyperintensivity.
Fig. 3. Ultrasound image of the right thyroid lobe with hypoechogenic nodule.
Fig. 4. Ultrasound image of the left thyroid lobe – small hypoechogenic nodules.

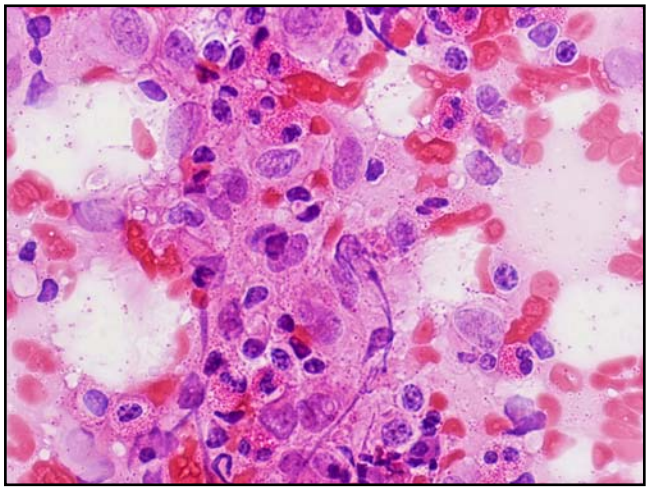


Fig. 5. FNAB result (hematoxylin and eosin staining, magnification – ×500); non-epithelial cells with the appearance of macrophages and few lymphocytes.

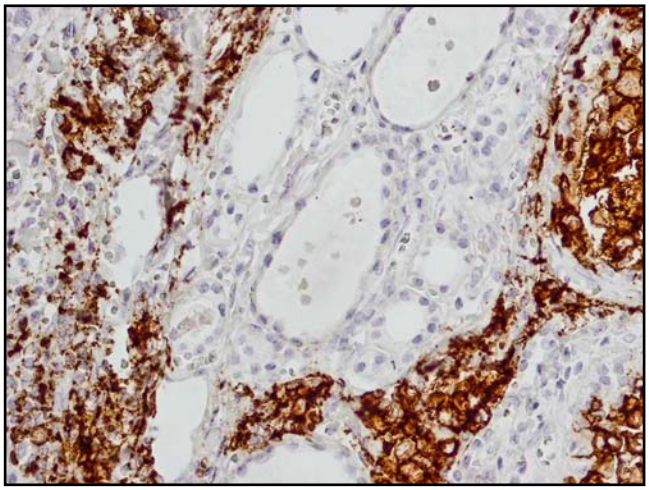


Fig. 6. Immunohistochemical staining – cells with immunophenotype CD1a (+) in the thyroid tissue (×300).

diabetes insipidus is the first or isolated presentation of LCH (Garcia Gallo *et al.* 2010). Moreover, the median time for the development of secondary localizations of LCH reaches even 9 years (Di Iorgi *et al.* 2015) – as it was in our patient. Except diabetes insipidus, other manifestations of hypothalamo-pituitary abnormalities in adult patients with LCH included: isolated GH/FSH-LH/TSH/ACTH deficiency or panhypopituitarism, as well as non-endocrine hypothalamic dysfunction – morbid obesity, short term memory deficits, sleeping disorders, disorders of thermoregulation and adipsia (Kaltsas *et al.* 2000). In our patient, LCH was manifested at the beginning – as anterior pituitary dysfunction with hyperprolactinemia and diabetes insipidus and afterwards – as goitre, however we cannot exclude that obesity is also a symptom of LCH, as a consequence of GH deficiency or hypothalamus failure (Kaltsas *et al.* 2000).

In the thyroid, LCH was presented as a painless enlargement, similarly to data from literature (Behrens *et al.* 2001, Patten *et al.* 2012, Chen *et al.* 2014). Most patients were euthyroid or hypothyroid, yet it was difficult to establish in our patient, since she was treated with L-thyroxine for central hypothyroidism. Also US image of thyroid tumour was similar to those reported earlier. All reported tumours were hypoechogenic, most of them were bilateral, without calcifications (Patten *et al.* 2012, Chen *et al*, 2014). The result of thyroid FNAB was difficult to interpretation; non-epithelial cells with the appearance of macrophages and few lymphocytes were revealed. Differential diagnosis of LCH located in the thyroid includes other much more common pathologies, benign – such as multinodular goitre, thyroiditis, cystic degeneration or malignant – such us undifferentiated carcinoma or lymphoma (Xia *et al.* 2012, Pusztaszeri *et al.* 2013,). It was previously noticed that LCH in thyroid coexisted with a thyroid carcinoma (Vergez *et al.* 2010). That is why false positive results are frequent (Garcia Gallo *et al.* 2010, Pusztaszeri *et al.* 2013). Finally diagnosis was determined on the basis of histopatological examination – positive immunohistochemical staining for CD1a and S-100.

Although endocrine presentations of LCH belong to low risk organ diseases, the optimal management is not clear, particularly in adults. We decided for surgical treatment of thyroid, which seemed to be optimal in the situation when we were not able to exclude malignant process in the thyroid gland. After the operation we excluded other foci of LCH with bone scintigraphy, computed tomography and US examination. Surgical treatment also resulted in total removal of pathological tissue, without the potential risk of chemiotherapy. Therefore, after the surgery we decided for "watchful waiting" policy since diabetes insipidus and hypopituitarism are generally permanent (Kaltsas *et al.* 2000, Garcia Gallo *et al.* 2010) and the chance of positive results of chemiotherapy was unlikely.

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Authors' contributions: *ES-J diagnosed and treated the patient, prepared of manuscript, SS and JS-D were responsible for histopatologic diagnosis and immunohistochemical staining, DB – carried out imaging studies, AL – senior author, supervised the patient and wrote the final version of the manuscript. All authors have read and approved the final manuscript.*

Competing interests: *The authors declare that they have no competing interests.*

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