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Interesting coincidence of atypical TSH-secreting pituitary adenoma and chronic lymphocytic leukemia

Niezwykłe współwystępowanie nietypowego guza przysadki wydzielającego TSH i przewlekłej białaczki limfatycznej

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Abstract

Thyrotropin-secreting adenomas (TSH-oma) are very rare pituitary tumours. They are macroadenomas usually presenting with signs and symptoms of hyperthyroidism, and mass effects. They can co-secrete other hormones such as growth hormone or prolactin. Different malignancies, including haematological ones, are reported in patients with pituitary diseases. Chronic lymphocytic leukemia (CLL) occurs mostly in older patients, more often in males. CLL is associated with increased risk of second malignancies such as other blood neoplasms, skin and solid tumours. We present a successful neurosurgical outcome in a patient with an interesting coincidence of atypical TSH-oma and asymptomatic CLL. **(Endokrynol Pol 2014; 65 (2): 144–147)**

Key words: *TSH-oma; chronic lymphocytic leukemia*

Streszczenie

Gruczolaki wydzielające TSH (TSH-oma) są rzadkimi guzami przysadki. Zwykle są makrogruczolakami dającymi objawy nadczynności tarczycy i następstwa masy guza. Mogą wydzielać także inne hormony, jak hormon wzrostu czy prolaktynę. U chorych z chorobami przysadki występują inne nowotwory, także układu krwionośnego. Przewlekła białaczka limfatyczna (CLL) występuje głównie u osób w starszym wieku, częściej u mężczyzn. Występowanie CLL wiąże się ze zwiększonym zagrożeniem innymi nowotworami: krwi, skóry, guzami litymi. W pracy przedstawiono opis skutecznego leczenia neurochirurgicznego pacjenta z interesującym współwystępowaniem nietypowego guza przysadki wydzielającego TSH oraz chorującego na bezobjawową postać CLL. **(Endokrynol Pol 2014; 65 (2): 144–147)**

Słowa kluczowe: *TSH-oma; przewlekła białaczka limfatyczna*

Introduction

Thyrotropin-secreting adenomas (TSH-oma) represent less than 1% of pituitary tumours. They are macroadenomas usually presenting with signs and symptoms of hyperthyroidism, and mass effects, while still being macroadenomas. They can co-secrete other hormones such as growth hormone (GH) or prolactin. In the hormonal diagnostics, elevated serum concentrations of thyroid hormones are accompanied by non-adequately normal or increased TSH secretion [1, 2]. The therapy of choice is selective transsphenoidal adenomectomy, with neurosurgery success rates of about 40%, due to the invasiveness and the fibrous character of the tumour. Somatostatin analogues can inhibit TSH secretion from the tumour and subsequently can lower thyroid hormones levels in 90% of cases. Sometimes symptomatic therapy with anti-thyroid drugs or radioiodine is necessary before surgery [1–4].

Different malignancies, including haematological ones, have been reported in patients with pituitary diseases, mainly in acromegaly [5, 6]. Moreover, other haematological disturbances have been observed in patients with prolactinoma, Sheehan's or Cushing's syndrome [7–9]. Acute leukemias have been observed in patients with acromegaly, craniopharyngioma, and Cushing's disease [9–12].

Chronic lymphocytic leukemia (CLL) is a haematologic malignancy originating from the bone marrow lymphocytes subsequently invading the peripheral blood. CLL occurs mostly in older patients, more often in males. In many cases, the patient remains asymptomatic for a long time, and a routine complete blood count (CBC) result indicates the possibility of the disease. There are different

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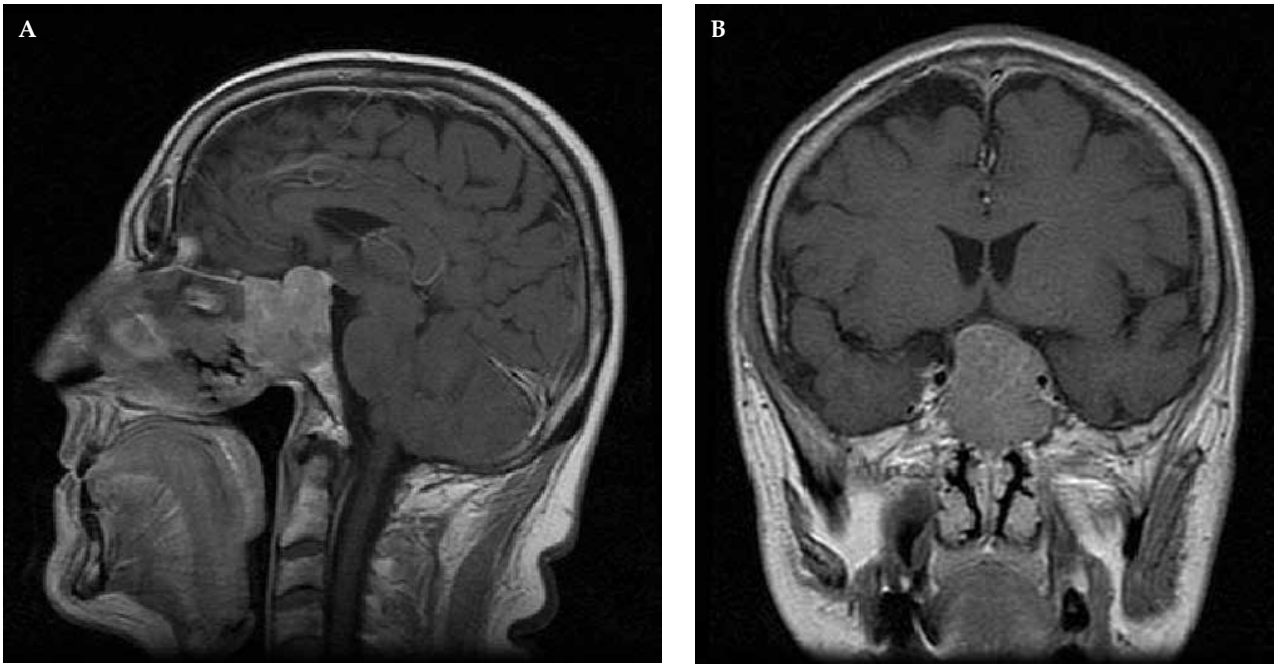

Figure 1. *Pituitary MRI scans presenting invasive pituitary macroadenoma of 3.5 cm diameter with left carotid sinus and skull-base invasion.* **A**. *sagittal;* **B**. *coronal*

Rycina 1. *Obraz MRI przysadki przedstawiający inwazyjny makrogruczolak przysadki o wymiarze 3,5 cm z naciekaniem lewej zatoki szyjnej i podstawy czaszki.* **A.** *projekcja strzałkowa;* **B.** *projekcja wieńcowa*

types and stages of the disease, influencing the therapy choice and prognosis. CLL is associated with increased risk of second malignancies such as other blood neoplasms, skin and solid tumours [13].

We present a successful neurosurgical outcome in a patient with an interesting coincidence of atypical TSH-oma and asymptomatic CLL.

Case report

A 59-year-old man with non-specific vision deterioration, left eye pain and headaches was examined by the neurologist and ophthalmologist, who confirmed bitemporal vision field deficits. Head CT suggested a pituitary lesion, and then pituitary MR scans revealed an invasive macroadenoma of 3.5 cm diameter with left carotid sinus and skull-base invasion (Fig. 1A and B). The patient reported body weight loss (7 kg during one year), irritability, restlessness, sleep and potency disturbances, and tachycardia. Symptomatic therapy using beta blocker was administered with moderate efficacy. Hormonal analyses showed elevated free thyroxine (fT4), normal TSH and low normal testosterone concentrations (Table I). Based on clinical symptoms, hormonal and MRI results, hyperthyroidism secondary to TSH secreting adenoma was diagnosed (Feb. 2009). The patient was administered anti-thyroid therapy (thiamazole 10 mg b.i.d.) and subsequently following fT4 normalisation submitted to transsphenoidal neurosurgery. After TSH secreting adenoma surgery (Fig. 2A and B), long-term normalisation of thyroid function (Table I) and cessation of clinical symptoms occurred (Mar. 2009). Hydrocortisone replacement therapy was necessary for the six month postsurgical period only.

Table I. ***Results of serum hormonal analyses in patient with TSH-oma before and after tumour surgery***

Tabela I. ***Wyniki badań hormonalnych w surowicy u pacjenta z TSH-oma przed i po operacji guza***

Hormone	Before surgery	After surgery	Normal range
TSH [mIU/mL]	2.99	1.6	0.4–4.0
fT4 [ng/mL]	2.58	1.4	0.9–1.8
testosterone [ng/mL]	2.15	3.1	2.6–6.5
prolactin [ng/mL]	18.8	5.5	1.9–20.0
GH [ng/mL]	–	0.1	0.05–2.0
IGF-1 [ng/mL]	–	152	81–225
ACTH [pg/mL]	–	26.7	0–46
LH [mU/L]	–	3.99	2.5–17
FSH [mU/L]	–	12.5	0.8–7.6

TSH — thyrotropin; fT4 — free thyroxine; GH — growth hormone; IGF-1 — insulin-like growth factor-1; ACTH — adrenocorticotropin; LH — luteinising hormone; FSH — follicle stimulating hormone

Histological report: pituitary adenoma with nuclear atypia. Immunohistochemistry: GH (++) — strong re-

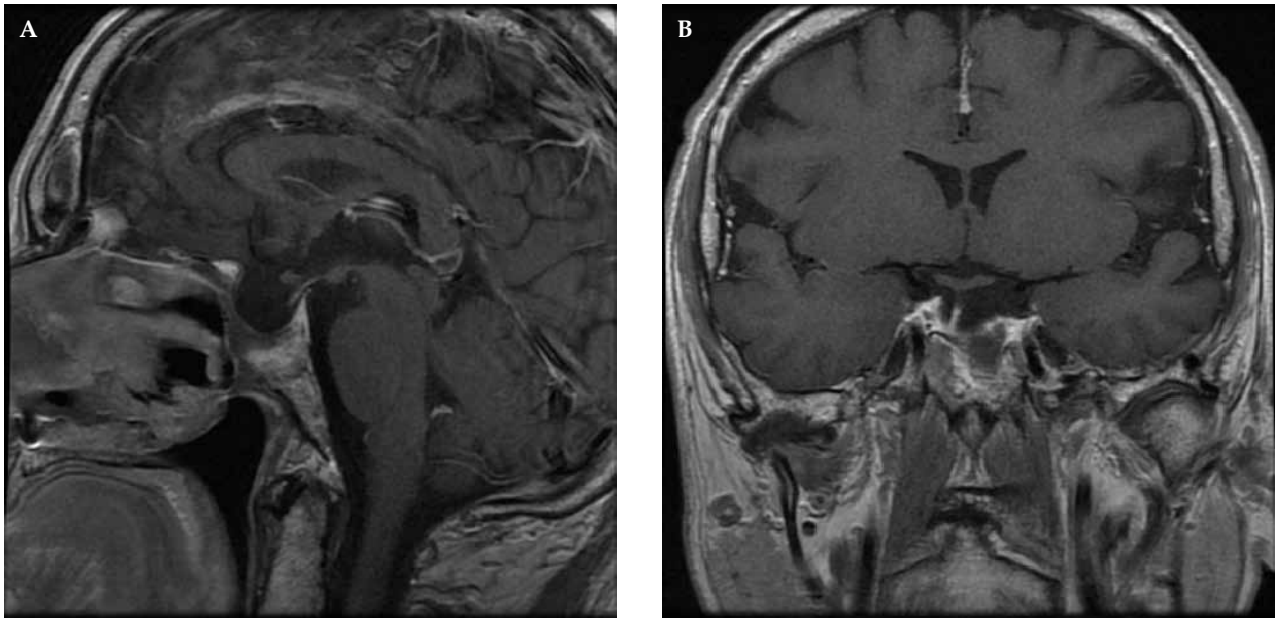

Figure 2. *Pituitary MRI scans after successful neurosurgery of TSH-secreting macroadenoma.* **A**. *sagittal;* **B**. *coronal*
Rycina 2. *Obraz MRI przysadki po skutecznej operacji guza wydzielającego TSH.* **A.** *projekcja strzałkowa;* **B.** *projekcja wieńcowa*

action in all cells, PRL (+/–) — in some cells, ACTH (–), TSH (+), FSH (–), LH (–), alpha subunit (+/–) — weak reaction in minority of cells, MIB1 < 3%; somatostatin receptors: sstr2A (++, strong membrane reaction), sstr5 (–). Electron microscopy — ultrastructural features of thyrotropic pituitary adenoma (Fig. 3, magn. 2,850 ×, Fig. 4, magn. 8,400 ×). Final conclusion: plurihormonal, monomorphic thyrotropic pituitary adenoma.

Five months later, the patient was examined again (Aug. 2009): normal thyroid function was observed, but for the first time an elevated lymphocytes percentage (79.9%) in blood count was discovered. Blood analysis was repeated later (Nov. 2010): elevated leukocytes and lymphocytes count, together with decreased haematocrit and haemoglobin, were shown again and the patient was submitted to the haematologist. Neither clinical symptoms (sweating, weight loss), lymphadenopathy, hepatosplenomegaly, nor haemorrhagic diathesis were noticed at that time.

CBC revealed: haemoglobin — 13.3 g%; haematocrit — 38.6%; red blood cells — 4.3 T/L; platelets — 78.9 G/L, white blood cells — 17.1 G/L. In the blood smear, mature cells lymphocytosis of 89.2% (19.65 G/L) was found. Myelogram showed the presence of mean density marrow, in which lymphocytes constituted 74%, erythrocytic 3.5% and granulocytic system 21% of nuclear cells. Immunophenotyping of medullar and blood cells revealed coexpression of CD5 and CD19 in 83% of the cells and positive CD23. Iliac bone marrow trephine biopsy revealed the presence of focal lymphocytic infiltration. Cytogenetic assessment of peripheral blood lymphocytes carried out by the FISH method did not present gene TP53 and ATM region aberration. Abdominal ultrasound and chest X-ray did not reveal lymphadenopathy. Based on the clinical and haematological picture, CLL in stadium IV according to Rai classification and grade C according to Binet classification was diagnosed.

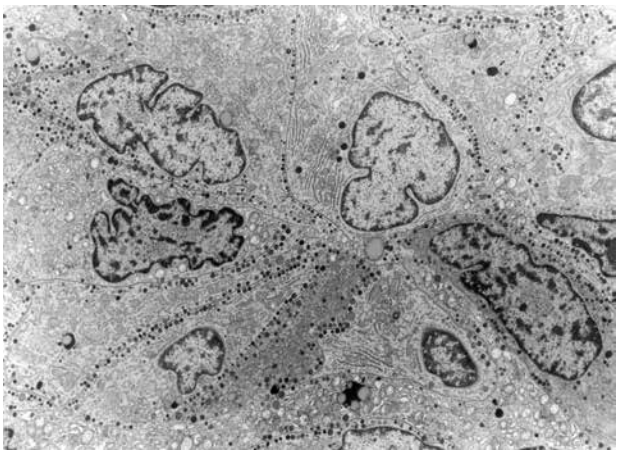

Figure 3. *Electron microscopy — ultrastructural features thyrotropic pituitary adenoma. Tumour has monomorphic character regarding ultrastructure (magn. 2,850×)*

Rycina 3. *Obraz w mikroskopie elektronowym — ultrastrukturalne cechy tyreotropowego gruczolaka przysadki. Guz ma charakter monomorficzny pod względem budowy ultrastrukturalnej (powiększenie 2850×)*

Until now (Nov. 2012) the patient has remained in our ambulatory follow-up without cytostatic therapy; he feels well, there are no laboratory or clinical symptoms of the progression of the CLL, nor recurrence of TSH-oma.

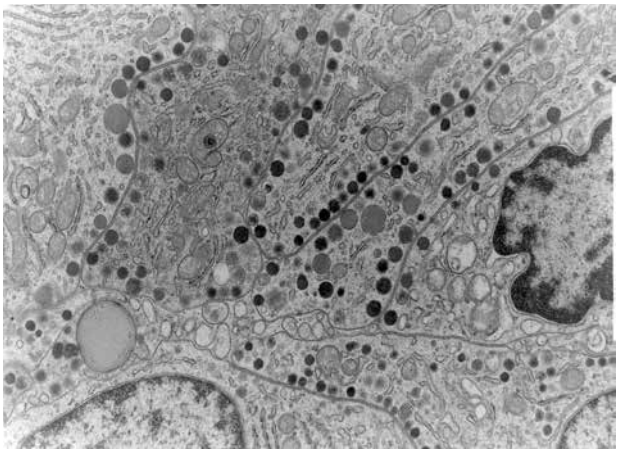

Figure 4. *Electron microscopy — two types of the secretory grains in cytoplasm: dense, smaller, circular circa 100–200 nm, located mainly just below cellular membrane, and larger ones circa 200–350 nm of smaller electron density, less numerous and dispersed in the cytoplasm. Smaller grains showed TSH content, and larger were typical for somatotropes and containing GH. The cells had large, multishape, irregular nuclei with considerable heterochromatin amount. Cytoplasm enclosed well-developed cellular organella, especially Golgi apparatus and rough endoplasmatic reticulum (magn. 8,400×)*

Rycina 4. *Obraz w mikroskopie elektronowym — w cytoplazmie widoczne dwa rodzaje ziarnistości wydzielniczych: gęste, drobniejsze, okrągłe, o średnicy około 100–200 nm, rozmieszczone głównie tuż pod błoną komórkową oraz większe, o średnicy około 200–350 nm i o mniejszej gęstości elektronowej ich zawartości; były one mniej liczne i rozproszone w cytoplazmie. Mniejsze ziarnistości wykazywały cechy ziarnistości zawierających TSH, a większe były charakterystyczne dla komórek somatotropowych i miały cechy ziarnistości gromadzących hormon wzrostu. Komórki miały duże, wielokształtne, nieregularne jądra ze znaczną ilością heterochromatyny. Cytoplazma zawierała dobrze rozwinięte organelle komórkowe, szczególnie aparat Golgiego i szorstką siateczkę endoplazmatyczną (powiększenie 8400×)*

Discussion

We present an unusual case of TSH-secreting pituitary adenoma in a male patient in whom asymptomatic CLL developed subsequently, incidentally discovered by routine CBC analysis. It is well known that CLL can be associated by other neoplasms, but to the best of our knowledge, no concomitant TSH-secreting pituitary tumour has been reported in the literature.

Our patient presented at the diagnosis with typical clinical symptoms and signs of hyperthyroidism together with sellar mass symptoms. Although based on histological, immunohistochemical (strong positive reaction for GH in all cells, weak positive reaction for TSH and plus/minus for prolactin and alpha-subunit in a minority of cells) and electron microscope analyses of the tumour (large secretory grains typical for somatotropes and containing GH), co-secretion of GH could be suspected, we did not observe any clinical symptoms of acromegaly. So, GH and IGF-1 serum concentrations were not analysed at the time of initial diagnosis. Moreover, following tumour surgery, there were observed normal levels of all pituitary hormones and regression of clinical symptoms. This would be rather doubtful in a case of clinically overt invasive GH- and TSH-cosecreting macroadenoma with carotid sinus and skull-base invasion. The 'silent' character of GH secretion might be taken into consideration in a reported case [14]. Strong membrane reaction of somatostatin receptors type 2A suggested a possible good reaction to somatostatin analogue therapy [1, 3, 4, 14]. This was not administered because of the necessity for urgent neurosurgery due to visual fields defects. We did not observe hyperprolactinaemia caused by stalk compression by macroadenoma, nor associated with PRL-secreting potential shown by immunohistochemistry, as in other cases of TSH-oma [1].

Today, 3.5 years after pituitary tumour surgery, and three years after documenting CLL, the patient is in a good general condition and requires no therapy because of the two diseases. There are no signs and symptoms of TSH-oma recurrence, nor other hormonal disturbances. Although the haematological assessment of the disease according to both classifications is high, neither symptoms nor clinical progression of CLL have been observed, and the patient remains without therapy.

Nevertheless, both the serious long-term prognosis of haematologic disorder and the potential risk of pituitary macroadenoma recurrence require careful follow-up of this patient.

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