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*Clinical case*

# SIPPLE SYNDROME OR MULTIPLE ENDOCRINE NEOPLASIA TYPE II

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***Abstract***

*Sipple syndrome is an autosomal-dominant combination of medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia, also known as multiple endocrine neoplasia type IIA. The aim is to discuss an interesting clinical case of Sipple syndrome or a multiple endocrine neoplasia type IIA. Clinical case: a 21-year-old woman presented complaining of hypertensive crisis and headaches. Examination subsequently revealed pheochromocytoma of the adrenal gland and hyperplasia of the thyroid gland. There are a number of clinical cases treating pituitary adenoma and pheochromocytoma in the literature. Experimental studies devoted to the identification of the relationship between the two tumors offer numerous theories, including random association, coincidence, or variants of multiple endocrine neoplasia (MEN) syndrome and the ectopic origin of pheochromocytoma. Due to the high risk of death associated with unidentified pheochromocytoma or thyroid cancer, all probable cases require careful attention. The patient underwent the following procedures: faslular-fascial lymphodissection, total thyroidectomy, laparoscopic left adrenalectomy, and cytological biopsy. The result of histological examination revealed medullary cancer of the right lobe of the thyroid gland with amyloid deposition, pT2pN0pM0 Stage II capsular invasion, and right parapental thyroid lobe hyperplasia. The final diagnosis was Sipple syndrome, MEN type IIA, medullary thyroid cancer pT2pN0pM0, Stage II, with left adrenal pheochromocytoma. The patient was recommended an oncologist and endocrinologist consultations in her hometown, the calcitonin and parathyroid hormones were controlled within 1 month, continue taking of Calcemin Advance before bedtime. Conclusion: we consider it expedient to analyze all clinical cases of MEN type IIA syndrome in the Kazakh population to evaluate the clinical course, the predictors of treatment, and the prognostic factors of medullary thyroid cancer.*

***Keywords:*** *Sipple syndrome, medullary thyroid cancer, pheochromocytoma, multiple endocrine neoplasia*

## Introduction

Sipple syndrome is an autosomal-dominant combination of medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia. Medullary thyroid cancer is the neoplasm in almost 100% of cases with multiple endocrine neoplasia (MEN) type II. Medullary thyroid cancer (MTC) with pheochromocytoma, parathyroid gland damage, and Gorlin syndrome, also known as multiple endocrine neoplasia type IIB, are distinguished in Sipple syndrome, also known as multiple endocrine neoplasia type IIA. Gorlin syndrome, along with pheochromocytoma and thyroid cancer, is diagnosed as multiple ganglioneuroma mucosa of the gastrointestinal tract [Ephimov A., 2007; Shuhei S., et al., 2001]. All patients with classic MEN type IIA and MEN type IIB with primary amyloidosis had codon 634 and 631 mutations, and codon 634, 609, 618, and 620 mutations with Hirschsprung's disease [Donis-Keller H. et al., 1993].

There is a clear link between medullary thyroid cancer and age from 5 to 25 years old (> 95%) with MEN II [Else Marie Opsahl, et al., 2016;]. MTC accounts for 4-10% of all thyroid carcinomas but represents up to 13.4% of thyroid cancer-related

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deaths [Gazizova D.O., et al., 2013; Papewalis C., et al., 2008]. Approximately 75% of MTC cases are sporadic with positive prognosis. Some 25% of MTC cases are hereditary forms characterized by faster progression and negative prognosis.

Treatment diagnostics consist of measuring the levels of adrenal, thyroid, and parathyroid gland hormones; measuring serum potassium and sodium; chest X-ray; computed tomography (CT) of the abdominal cavity and retroperitoneal space; ultrasound and thyroid biopsy; and cytomorphological studies, among others [Shuhei S. et al., 2001; Zhuraev ShSh et al., 2009].

The main clinical types of MTC are sporadic MTC (70-80%) and hereditary MTC (20-30%), which manifests as MEN IIA syndrome (Sipple) in 20-25% of cases, MEN IIB syndrome (Gorlin) in 2-5% of cases, and the familial (isolated) form of MTC in 70-80% of cases [Younis E., 2017].

Pheochromocytoma is the second most frequently occurring tumor with MEN type II. It is located in the adrenal glands and most often affects one of them. It usually develops at the ages of 35-45 years [W. Keat Ch. et al., 2002].

## Report

Patient E. was a 21-year-old woman who was admitted to JSC National Scientific Center of Surgery on a planned basis. The patient had been complaining of an increase in blood pressure under 200/100 mm Hg and headache.

Anamnesis morbid: The patient considered herself ill during the previous year, with the sudden appearance of nausea, vomiting, headache, dizziness, palpitation, and growing weakness. Admitted to medical care, she presented with an increase in blood pressure under 200/100 mm Hg, was diagnosed as being in hypertensive crisis, and was hospitalized in her hometown of Aktobe. Abdominal and retroperitoneal space CT revealed a formation in the left adrenal gland. Patients with left adrenal gland pheochromocytoma, hypertonic crisis, and thyroid gland hyperplasia are sent for surgical treatment to the Department of Endocrine Surgery of JSC National Scientific Center of Surgery.

Anamnesis vitae: The patient was born at full-term with a normal birth weight. She grew and developed normally. As a child, she was treated for tuberculosis and was considered cured. Hereditarily, she was burdened with papillary thyroid cancer from her mother's lineage and adrenal gland pheochromocytoma from her father's lineage. She was treated with surgery (thyroidectomy and left adrenalectomy).

Physical exams: The patient was generally healthy, was alert and thinking logically and coherently, was physically active, and had moderately moist skin and sclera with normal color. She was characterized as having a normosthenic body type. Her nutritional status was satisfactory. Her musculoskeletal system had no pathology, and her lymph nodes had no palpable masses. Her thyroid was palpable with right lobe formation, with a tight elastic nodule under 2.0 cm. An examination of her lungs revealed vesicular breath sounds and no wheezing.

She had muffled heart sounds and sinus rhythm. Her BP was 135/85 mm Hg and pulse was 92 beats per minute. No pathology was found in her other organs and systems. In her adrenal glands, cortisol was 421 nmol / l and aldosterone was 38.7 pg / ml.

Pheochromocytoma was diagnosed by measuring the patient's metanephrine levels; her adrenaline was 11884 pg / ml (normal is 74-297 pg / ml). Her normetanephrine level was noradrenalinum 16887 pg / ml (normal is 105-354 pg / ml), and dopamine was 85 pg / ml. Her thyroid hormone level was TSH -0.924. A chest X-ray revealed no pathology. An abdominal ultrasound found biliary dyskinesia and a bend in the gallbladder, chronic cholecystitis, diffuse parenchyma changes of the pancreas, and left adrenal gland formation. An abdominal and retroperitoneal space CT showed volume formation in the left adrenal gland (Figure 1). Esophagogastroduodenoscopy (EGD) revealed signs of superficial gastritis.

Ultrasound of the thyroid gland revealed it was enlarged: the left lobe was 4.2 x 1.5 x 1.4 cm, the isthmus was 0.3 cm, and the volume was 8.82 ml. The right lobe was 4.7 x 1.9 x 1.8 cm, volume 16.07 ml, the total volume of the gland was 24.8 ml. The

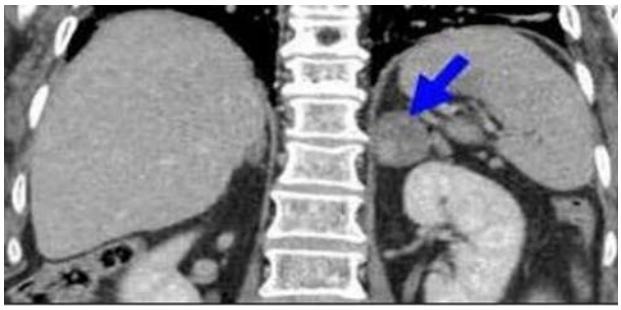

***Figure 1.*** *An abdominal and retroperitoneal CT shows pheochromocytoma and volume formation in the left adrenal gland.*

contours of the thyroid gland were even and clear, and the echogenicity of the lobes had not changed. The structure of the parenchyma was uniform, the hypoechoic right lobe formation was 1.8 x 1.2 x 1.3 cm, and the contours were clear and uneven. There were several fuzzy sections along the front walls. In the structure of 4-5 echoes of dense inclusions up to 0.2-0.3 cm long, a fuzzy acoustic shadow was behind them are. Color Doppler flow imaging found per- and intranodular vascularization. The regional lymph nodes had not changed. The parathyroid glands were not visualized. The result of the thyroid biopsy was follicular epithelium polymorphic cell proliferation and nuclei conglomeration. The cytogram aroused suspicions of follicular neoplasia, and the oxyphilic cell adenoma was not expressed. An endocrinologist's exam confirmed the diagnosis of left pheochromocytoma, mononodular euthyroid goiter.

The patient underwent the following procedures: faslular-fascial lymphodissection, total thyroidectomy, laparoscopic left adrenalectomy, and cytological biopsy.

The result of histological examination revealed medullary cancer of the right lobe of the thyroid gland with amyloid deposition, pT2pN0pM0 Stage II capsular invasion, and right parapental thyroid lobe hyperplasia (ICD-O: 8345 / 3). A polymorphous follicular colloid goiter was found in the left lobe of the thyroid (Figure 2).

The result of the adrenal gland histological examination confirmed the alveolar-trabecular variant of pheochromocytoma of the left adrenal gland (ICD-O: 8700 / 1) (Figure 3).

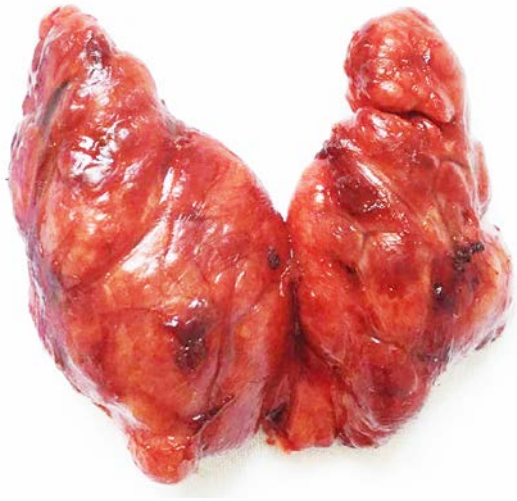

***Figure 2.*** *Postoperative thyroid gland material showing medullary thyroid cancer pT2pN0pM0, Stage II.*

The postoperative period was stable and without complications. According to control tests, a decrease in total calcium to 1.13 mmol / l (a rate of 2.10-2.55 mmol / l) was found in the postoperative period. The calcitonin level was 130.8 pg / ml (normal is less than 13 pg / ml). The level of parathyroid hormone was 2.85 pmol / l at a rate of 1.6-6.9 pmol / l). The potassium level was 3.3 mmol / l and sodium was 136 mmol / l.

At the time of discharge, the patient had no complaints, and her general condition was satisfactory. Objectively, the examination did not reveal any pathology, the postoperative wounds healed with primary tension, and drainage from the abdominal cavity ceased.

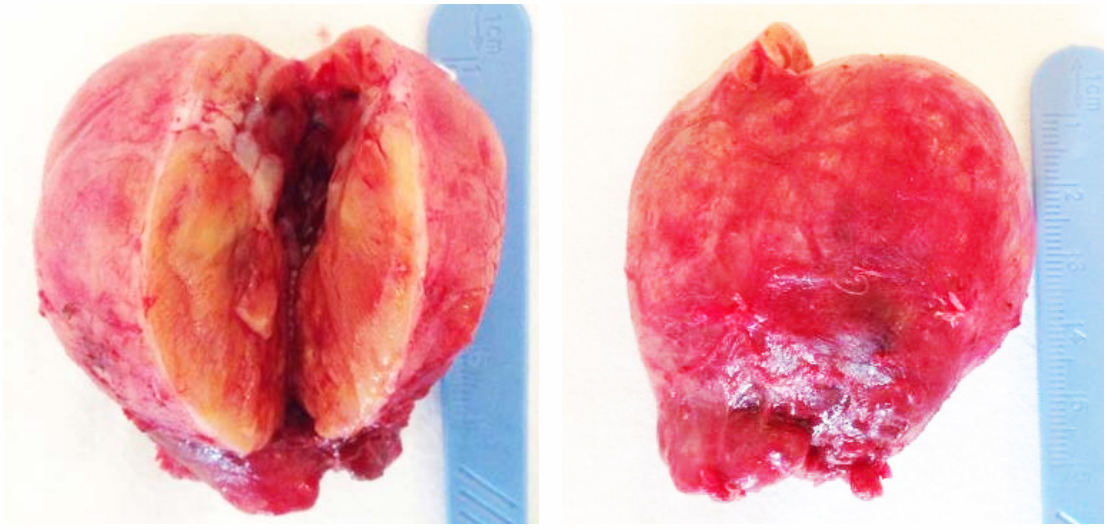

***Figure 3.*** *Pheochromocytoma. A: Postoperative pathomorphology material of the left adrenal gland. B: Cutaway view of the adrenal gland*

The final diagnosis was Sipple syndrome, MEN type IIA, medullary thyroid cancer pT2pN0pM0, Stage II, with left adrenal pheochromocytoma.

The patient was recommended an oncologist and endocrinologist consultations in her hometown. She was prescribed 100 mg of L-thyroxine daily, and after 3 months the TSH test was repeated and the hormone dose adjusted. The calcitonin and parathyroid hormones were controlled within 1 month. Tevabon was recommended for 3 months, then repeat doses of vitamin D and calcium solved the problem of long-term treatment. Once a year it was necessary to monitor her calcitonin and adrenal glands via dynamic computed tomography. She continued taking 1 tablet of Calcemin Advance before bedtime. Monitoring for RET-proto-oncogenes was done in case of the confirmation of the presence of a mutation in her first-degree relatives.

**Discussion**

At present, the early diagnosis of disease before hospitalization is urgent. Hereditary forms of medullary carcinomas necessitate family genetic screening and preventive thyroidectomy, as confirmed by the case described herein [Michael E. G., et al., 2004; Xavier M. et al., 2014]. It is important to assess the rate of increase, rather than the absolute value of calcitonin, since this is the most important sign of tumor progression. Calcitonin levels need to be evaluated every 6 months. If the level of calcitonin is maintained, the distant metastases search should be repeated with the goal of their excision. A slow rise in calcitonin levels indicates the prognosis is good [Michael E. G., et al., 2004; James C. S. et al., 2008]

In conclusion, we consider it expedient to analyze all clinical cases of MEN type IIA syndrome in the Kazakh population to evaluate the clinical course, the predictors of treatment, and the prognostic factors of medullary thyroid cancer.

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